(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 January 2004 (08.01.2004)

PCT

(10) International Publication Number
WO 2004/003147 A2

(51) International Patent Classification[7]: C12N

(21) International Application Number:
PCT/US2003/020025

(22) International Filing Date: 25 June 2003 (25.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/391,834 27 June 2002 (27.06.2002) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/003147 A2

(54) Title: CNGH0004 POLYPEPTIDES, ANTIBODIES, COMPOSITIONS, METHODS AND USES

(57) Abstract: The present invention relates to at least one novel CNGH0004 polypeptides, antibodies, including isolated nucleic acids that encode at least one CNGH0004 polypeptide or antibody, CNGH0004 vectors, host cells, transgenic animals or plants, and methods of making and using thereof, including therapeutic compositions, methods and devices.

CNGH0004 POLYPEPTIDES, ANTIBODIES, COMPOSITIONS, METHODS AND USES

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to at least one CNGH0004 polypeptide or fragment thereof, and antibodies and anti-idiotype antibodies specific therefore, as well as nucleic acids encoding such CNGH0004 polypeptides, fragments, antibodies, complementary nucleic acids, vectors, host cells, and methods of making and using thereof, including therapeutic formulations, administration and devices.

RELATED ART

Psoriasis is a genetic, multifactorial, chronic inflammatory skin disease, with a prevalence of 2.6% of the US population. The disease is characterized by pronounced hyperproliferation of keratinocytes, which results in rapid epidermal turnover and thickened, scaly, red plaques observed clinically. Other prominent histopathological features of the disease are alterations of cytokine production, fibroblast activation, vascular expansion, and leukocyte infiltration in the dermis and epidermis. Dysregulation in cytokine production from both activated cells in the dermis and the immune cells seems to play an important role in mediating the inflammatory events associated with psoriasis. To this end, a number of changes in gene and/or protein expression have been described previously in psoriasis and some of these genes and/or proteins have also been found to be associated with other inflammatory diseases. These include proinflammatory cytokines such as IL-1 and TNFα, adhesion molecules such as intercellular adhesion molecule 1 (ICAM1) and vascular adhesion molecule 1 (VCAM1), chemokines, and defensins. Recently, gene expression microarray technology has been applied to profile gene expression patterns in normal versus psoriatic lesional skins on a more inclusive scale and has provided new insights to the pathogenesis of psoriasis.

cDNA microarray technology provides a format for the simultaneous measurement of the expression level of thousands of genes in a single hybridization assay. It is also amenable to an automated, high-throughput format. More importantly, microarray technology can be used to discover new genes, quantify and analyze gene expression and assign functionality to genes with unknown function. With the complete sequencing of human genome, identification and cloning of new genes is now accomplished rapidly. However, to understand whether these genes encode new proteins or to further identify function of these new proteins has not been advanced as rapidly. The impediment has become one of the main reasons for the use of high throughput cDNA microarray technology in a well-

designed experimental setting to discover novel protein-encoding genes or genes with novel function that may subsequently become potential therapeutic targets for a variety of human diseases.

Accordingly, there is a need to provide CNGH0004 polypeptides or antibodies or fragments that overcome one or more of these problems, as well as improvements over known polypeptides or antibodies or fragments thereof.

SUMMARY OF THE INVENTION

This invention discloses the discovery of a novel CNGH0004 gene and polypeptides through data analysis of the microarray gene expression profiling in psoriatic lesional skin biopsy samples obtained from infliximab (REMICADE®, an anti-TNFα monoclonal antibody approved to treat rheumatoid arthritis and Crohn's disease) treated versus placebo treated patients. The invention sets forth sequences coding for a gene designated CNGH0004, and presents evidence for said gene the roles of a developmental and tissue remodeling regulator and as a tumor specific marker. Said sequences include nucleic acid sequences of full-length cDNA, open reading frames (ORFs), probes (e.g. for PCR), antisense, ribozymes, and vectors containing the sequences and the polypeptides encoded by them.

Compositions and methods for the therapy and diagnosis of, as non-limiting examples, psoriasis, rheumatoid arthritis, Crohn's disease, asthma, and cancer, as well as other CNGH0004 related diseases and disorders, as described herein or as known in the art. Compositions may comprise one or more protein isoforms, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses CNGH0004 protein, or a T cell that is specific for cells expressing a polypeptide encoded by the gene. Such compositions may be used, for example, for the prevention and treatment of diseases such as psoriasis, asthma, and brain-, colon-, skin- and/or breast cancer. Diagnostic and prognostic methods based on detecting CNGH0004 protein, or mRNA encoding such a protein, in a sample are also disclosed.

The present invention provides isolated CNGH0004 polypeptides and encoding nucleic acid, as well as CNGH0004 human, primate, rodent, mammalian, chimeric, or human CNGH0004 polypeptides, antibodies, immunoglobulins, cleavage products and other specified portions and variants thereof, as well as CNGH0004 polypeptide or anibody compositions, encoding or complementary nucleic acids, vectors, host cells, compositions, formulations, devices, transgenic animals, transgenic plants, and methods of making and using thereof, as described and enabled herein, in combination with what is known in the art.

The present invention also provides at least one isolated CNGH0004 antibody as described herein. An antibody according to the present invention can include any polypeptide or peptide

containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one complementarity determining region (CDR) (also termed the hypervariable region or HV) of a heavy or light chain variable region, or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, wherein the antibody can be incorporated into an antibody of the present invention. An antibody of the invention can include or be derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, or any combination thereof, and the like.

The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, or hybridizing to, a polynucleotide encoding specific CNGH0004 polypeptides or antibodies, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising at least ibe if said CNGH0004 polypeptide or antibody encoding or complementary nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such antibody nucleic acids, vectors and/or host cells.

At least one antibody of the invention binds at least one specified epitope specific to at least one CNGH0004 polypeptide, subunit, fragment, portion or any combination thereof. The at least one epitope can comprise at least one antibody binding region that comprises at least one portion of said polypeptide, which epitope is preferably comprised of at least 1-5 amino acids of at least one portion thereof, such as but not limited to, at least one functional, extracellular, soluble, hydrophillic, external or cytoplasmic domain of said polypeptide, or any portion thereof.

The at least one antibody can optionally comprise at least one specified portion of at least one complementarity determining region (CDR) (e.g., CDR1, CDR2 or CDR3 of the heavy or light chain variable region) and optionally at least one constant or variable framework region or any portion thereof. The at least one antibody amino acid sequence can further optionally comprise at least one specified substitution, insertion or deletion as described herein or as known in the art.

The present invention also provides at least one isolated CNGH0004 polypeptide or antibody as described herein, wherein the antibody has at least one activity. An CNGH0004 polypeptide antibody can thus be screened for a corresponding activity according to known methods, such as but not limited to, at least one biological activity towards a CNGH0004 polypeptide or polypeptide related function.

The present invention further provides at least one CNGH0004 anti-idiotype antibody to at least one CNGH0004 antibody of the present invention. The anti-idiotype antibody includes any

polypeptide or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one complementarity determining region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion thereof, that can be incorporated into an antibody of the present invention. An antibody of the invention can include or be derived from any mammal, such as but not limited to a human, a mouse, a rabbit, a rat, a rodent, a primate, and the like. The present invention provides, in one aspect, isolated nucleic acid molecules comprising, complementary, or hybridizing to, a polynucleotide encoding at least one CNGH0004 anti-idiotype antibody, comprising at least one specified sequence, domain, portion or variant thereof. The present invention further provides recombinant vectors comprising said CNGH0004 anti-idiotype antibody encoding nucleic acid molecules, host cells containing such nucleic acids and/or recombinant vectors, as well as methods of making and/or using such anti-idiotype antiobody nucleic acids, vectors and/or host cells.

The present invention also provides at least one method for expressing at least one CNGH0004 polypeptide or antibody, or CNGH0004 anti-idiotype antibody, in a host cell, comprising culturing a host cell as described herein under conditions wherein at least one CNGH0004 antibody is expressed in detectable and/or recoverable amounts.

The present invention also provides at least one composition comprising (a) an isolated CNGH0004 polypeptide or antibody encoding nucleic acid and/or polypeptide or antibody as described herein; and (b) a suitable carrier or diluent. The carrier or diluent can optionally be pharmaceutically acceptable, such as but not limited to known carriers or diluents. The composition can optionally further comprise at least one further compound, polypeptide or composition.

The present invention further provides at least one CNGH0004 polypeptide or antibody method or composition, for administering a therapeutically effective amount to modulate or treat at least one CNGH0004 related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein.

The present invention also provides at least one composition, device and/or method of delivery of a therapeutically or prophylactically effective amount of at least one CNGH0004 polypeptide or antibody, according to the present invention.

The present invention further provides at least one CNGH0004 polypeptide or antibody method or composition, for diagnosing at least one CNGH0004 related condition in a cell, tissue, organ, animal or patient and/or, prior to, subsequent to, or during a related condition, as known in the art and/or as described herein.

The present invention also provides at least one composition, device and/or method of delivery for diagnosing of at least one CNGH0004 polypeptide or antibody, according to the present invention.

In another aspect, the present invention provides at least one isolated mammalian CNGH0004 polypeptide, comprising the amino acid sequences as part of SEQ ID NO:1.

Also provided is an isolated nucleic acid encoding at least one isolated mammalian CNGH0004 polypeptide; an isolated nucleic acid vector comprising the isolated nucleic acid, and/or a prokaryotic or eukaryotic host cell comprising the isolated nucleic acid. The host cell can optionally be at least one selected from prokaryotic or eukaryotic cells, or fusion cells thereof, e.g., but not limited to, mammalian, plant or insect, such as but not limited to, CHO, myeloma, or lymphoma cells, bacterial cells, yeast cells, silk worm cells, or any derivative, immortalized or transformed cell thereof. Also provided is a method for producing at least one CNGH0004 polypeptide, comprising translating the polypeptide encoding nucleic acid under conditions in vitro, in vivo or in situ, such that the CNGH0004 polypeptide is expressed in detectable or recoverable amounts.

Also provided is a composition comprising at least one isolated mammalian CNGH0004 polypeptide and at least one pharmaceutically acceptable carrier or diluent. The composition can optionally further comprise an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplactic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

Also provided is a method for diagnosing or treating a CNGH0004 related condition in a cell, tissue, organ or animal, comprising

(a) contacting or administering a composition comprising an effective amount of at least one isolated mammalian CNGH0004 polypeptide of the invention with, or to, the cell, tissue, organ or animal. The method can optionally further comprise using an effective amount of 0.0000001-500 mg/kilogram per: 1-24 hours, 1-7 days, 1-52 weeks, 1-24 months, 1-30 years (or any range or value

therein), of the cells, tissue, organ or animal. The method can optionally further comprise using the contacting or the administrating by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal. The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or protein selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplactic, an immunomodulation drug, an opthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, an anti-inflammatory, a non-steroid inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

Also provided is at least one medical device, comprising at least one isolated mammalian CNGH0004 polypeptide of the invention, wherein the device is suitable to contacting or administerting the at least one CNGH0004 polypeptide by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

Also provided is an article of manufacture for human pharmaceutical or diagnostic use,

comprising packaging material and a container comprising a solution or a lyophilized form of at least one isolated mammalian CNGH0004 polypeptide of the present invention. The article of manufacture can optionally comprise having the container as a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

Also provided is a method for producing at least one isolated mammalian CNGH0004 polypeptide of the present invention, comprising providing a host cell or transgenic animal or transgenic plant or plant cell capable of expressing in recoverable amounts the polypeptide. Further provided in the present invention is at least one CNGH0004 polypeptide produced by the above method.

In another aspect the present invention provides at least one isolated mammalian CNGH0004 antibody, comprising at least one human CDR, wherein the antibody specifically binds at least one epitope comprising at least 1-3, to the entire amino acid sequence of SEQ ID NO:1.

The at least one antibody can optionally further comprise at least one characteristic selected from: (i) bind CNGH0004 with an affinity of at least one selected from at least 10^{-9} M, at least 10^{-10} M, at least 10^{-11} M, or at least 10^{-12} M; and/or (ii) substantially neutralizes at least one activity of at least one CNGH0004 polypeptide. Also provided is an isolated nucleic acid encoding at least one isolated mammalian CNGH0004 antibody; an isolated nucleic acid vector comprising the isolated nucleic acid, and/or a prokaryotic or eukaryotic host cell comprising the isolated nucleic acid. The host cell can optionally be at least one selected from prokaryotic or eukaryotic cells, or fusion cells thereof, e.g., but not limited to, mammalian, plant or insect, such as but not limited to, CHO, myeloma, or lymphoma cells, bacterial cells, yeast cells, silk worm cells, or any derivative, immortalized or transformed cell thereof. Also provided is a method for producing at least one CNGH0004 antibody, comprising translating the antibody encoding nucleic acid under conditions in vitro, in vivo or in situ, such that the CNGH0004 antibody is expressed in detectable or recoverable amounts.

Also provided is a composition comprising at least one isolated mammalian CNGH0004 antibody and at least one pharmaceutically acceptable carrier or diluent. The composition can optionally further comprise an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, an anti-infective drug, a cardiovascular (CV) system drug,

a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplactic, an immunomodulation drug, an opthalmic, otic or nasal drug, a topical drug, a nutritional drug , a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a growth hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

The present invention further provides an anti-idiotype antibody or fragment that specifically binds at least one isolated mammalian CNGH0004 antibody of the present invention.

Also provided is a method for diagnosing or treating a CNGH0004 related condition in a cell, tissue, organ or animal, comprising

(a) contacting or administering a composition comprising an effective amount of at least one isolated mammalian CNGH0004 antibody of the invention with, or to, the cell, tissue, organ or animal. The method can optionally further comprise using an effective amount of 0.0001-500 mg/kilogram of the cells, tissue, organ or animal. The method can optionally further comprise using the contacting or the administrating by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or polypeptide selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplactic, an immunomodulation drug, an opthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. The method can optionally further comprise administering, prior, concurrently or after the (a) contacting or administering, at least one composition

comprising an effective amount of at least one compound or protein selected from at least one of a detectable label or reporter, a TNF antagonist, an antirheumatic, a muscle relaxant, a narcotic, an anti-inflammatory, a non-steroid inflammatory drug (NTHE), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial, an antipsoriatic, a corticosteriod, an anabolic steroid, an erythropoietin, an immunization, an immunoglobulin, an immunosuppressive, a hormone, a hormone replacement drug, a radiopharmaceutical, an antidepressant, an antipsychotic, a stimulant, an asthma medication, a beta agonist, an inhaled steroid, an epinephrine or analog, a cytokine, or a cytokine antagonist.

Also provided is at least one medical device, comprising at least one isolated mammalian CNGH0004 antibody of the invention, wherein the device is suitable to contacting or administerting the at least one CNGH0004 antibody by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

Also provided is an article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising a solution or a lyophilized form of at least one isolated mammalian CNGH0004 antibody of the present invention. The article of manufacture can optionally comprise having the container as a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

Also provided is a method for producing at least one isolated mammalian CNGH0004 antibody of the present invention, comprising providing a host cell or transgenic animal or transgenic plant or plant cell capable of expressing in recoverable amounts the antibody. Further provided in the present invention is at least one CNGH0004 antibody produced by the above method.

The present invention further provides any invention described herein.

DESCRIPTION OF THE INVENTION

The present invention provides isolated, recombinant and/or synthetic human CNGH0004 protein, as well as human, primate, rodent, mammalian, chimeric, humanized or CDR-grafted, antibodies and CNGH0004 anti-idiotype antibodies thereto, and compositions and encoding nucleic acid molecules comprising at least one polynucleotide encoding at least one CNGH0004 protein, antibody or anti-idiotype antibody. The present invention further includes, but is not limited to, methods of making and using such nucleic acids and antibodies and anti-idiotype antibodies, including diagnostic and therapeutic compositions, methods and devices.

As used herein, an "CNGH0004 antibody," "CNGH0004 antibody," and the like include any polypeptide or peptide containing molecule that comprises at least a portion of an immunoglobulin molecule, such as but not limited to at least one complementarity determinng region (CDR) of a heavy or light chain or a ligand binding portion thereof, a heavy chain or light chain variable region, a heavy chain or light chain constant region, a framework region, or any portion , fragment or variant thereof, or at least one portion of an CNGH0004 receptor or binding polypeptide, which can be incorporated into a CNGH0004 antibody of the present invention.

Antibodies can include one or more of at least one CDR, at least one variable region, at least one constant region, at least one heavy chain (e.g., γ_1, γ_2, γ_3, γ_4, μ, α_1, α_2, δ, ε), at least one light chain (e.g., κ and λ), or any portion or fragment thereof, and can further comprise interchain and intrachain disulfide bonds, hinge regions, glycosylation sites that can be separated by a hinge region, as well as heavy chains and light chains. Light chains typically have a molecular weight of about 25Kd and heavy chains typically range from 50K-77Kd. Light chains can exist in two distinct forms or isotypes, kappa (κ) and lambda (λ), which can combine with any of the heavy chain types. All light chains have at least one variable region and at least one constant region. The IgG antibody is considered a typical antibody structure and has two intrachain disulfide bonds in the light chain (one in variable region and one in the constant region), with four in the heavy chain, and such bond encompassing a peptide loop of about 60-70 amino acids comprising a "domain"of about 110 amino acids in the chain. IgG antibodies can be characterized into four classes, IgG1, IgG2, IgG3 and IgG4. Each immunoglobulin class has a different set of functions. The following table summarizes the Physicochemical properties of each of the immunoglobuling classes and subclasses.

Property	IgG1	IgG2	IgG3	IgG4	IgM	IgA1	IgA2	SIgA	IgD	IgE
Heavy Chain	γ1	γ1	γ1	γ1	μ	α1	α2	α1 / α2	δ	e
Mean Serum conc. (mg/ml)	9	3	1	0.5	1.5	3.0	0.5	0.05	0.03	0.00005

Sedimentation constant	7s	7s	7s	7s	19s	7s	7s	11s	7s	8s
Mol. Wt. (X 10^3)	146	146	170	146	970	160	160	385	184	188
Half Life (days)	21	20	7	21	10	6	6	?	3	2
% intravascular distribution	45	45	45	45	80	42	42	Trace	75	50
Carbohydrate (%)	2-3	2-3	2-3	2-3	12	7-11	7-11	7-11	9-14	12

The following table summarizes non-limiting examples of antibody effector functions for human antibody classes and subclasses.

Effector function	IgG1	IgG2	IgG3	IgG4	IgM	IgA	IgD	IgE
Complement fixation	++	+	+++	–	+++	–	–	-
Placental transfer	+	+	+	+	-	-	-	-
Binding to Staph A	+++	+++	-	+++	-	-	-	-
Binding to Strep G	+++	+++	+++	+++	-	-	-	-

Accordingly, the type of antibody or fragment thereof can be selected for use according to the present invention based on the desired characteristics and functions that are desired for a particular therapeutic or diagnostic use, such as but not limited to serum half life, intravascular distribution, complement fixation, etc.

Antibody diversity is generated by at least 5 mechanisms, including (1) the use of multiple genes encoding parts of the antibody; (2) somoatic mutation, e.g., primordial V gene mutation during B-cell ontogeny to produce different V genes in different B-cell clones; (3) somatic recombination, e.g., gene segments J1-Jn recombine to join the main part of the V-region gene during B-cell ontogeny; (4) gene conversion where sections of DNA from a number of pseudo V region can be copied into the V region to alter the DNA sequence; and (5) nucleotide addition, e.g., when V and J regions are cut, before joining, and extra nucleotides may be inserted to code for additional amino acids. Non-limiting examples include, but are not limited to, (i) the selection/recombination of Vκ, J, and Cκ regions from germ line to B-cell clones to generate kappa chains; (ii) selection/recombination of Vλ, J, and Cλ regions from germ line to B-cell clones to generate lambda chains; (iii) selection/recombination of V_H, D1-D30 and J_H1-J_H6 genes to form a functional VDJ gene encoding a heavy chain variable region. The above mechanisms work in a coordinated fashion to generate antibody diversity and specificity.

The term "antibody "is further intended to encompass antibodies, digestion fragments, specified portions and variants thereof, including antibody mimetics or comprising portions of antibodies that mimic the structure and/or function of an antibody or specified fragment or portion thereof, including single chain antibodies and fragments thereof. Functional fragments include antigen-binding fragments that bind to a mammalian CNGH0004. For example, antibody fragments

capable of binding to CNGH0004 or portions thereof, including, but not limited to Fab (e.g., by papain digestion), Fab' (e.g., by pepsin digestion and partial reduction) and $F(ab')_2$ (e.g., by pepsin digestion), facb (e.g., by plasmin digestion), pFc' (e.g., by pepsin or plasmin digestion), Fd (e.g., by pepsin digestion, partial reduction and reaggregation), Fv or scFv (e.g., by molecular biology techniques) fragments, are encompassed by the invention (see, e.g., Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001)).

Such fragments can be produced by enzymatic cleavage, synthetic or recombinant techniques, as known in the art and/or as described herein. Antibodies can also be produced in a variety of truncated forms using antibody genes in which one or more stop codons have been introduced upstream of the natural stop site. For example, a combination gene encoding a $F(ab')_2$ heavy chain portion can be designed to include DNA sequences encoding the CH_1 domain and/or hinge region of the heavy chain. The various portions of antibodies can be joined together chemically by conventional techniques, or can be prepared as a contiguous polypeptide using genetic engineering techniques.

As used herein, the term "human antibody" refers to an antibody in which substantially every part of the polypeptide (e.g., CDR, framework, C_L, C_H domains (e.g., C_H1, C_H2, C_H3), hinge, (V_L, V_H)) is substantially non-immunogenic in humans, with only minor sequence changes or variations. Similarly, antibodies designated primate (monkey, babboon, chimpanzee, etc.), rodent (mouse, rat, rabbit, guinea pid, hamster, and the like) and other mammals designate such species, sub-genus, genus, sub-family, family specific antibodies. Further, chimeric antibodies include any combination of the above. Such changes or variations optionally and preferably retain or reduce the immunogenicity in humans or other species relative to non-modified antibodies. Thus, a human antibody is distinct from a chimeric or humanized antibody. It is pointed out that a human antibody can be produced by a non-human animal or prokaryotic or eukaryotic cell that is capable of expressing functionally rearranged human immunoglobulin (e.g., heavy chain and/or light chain) genes. Further, when a human antibody is a single chain antibody, it can comprise a linker peptide that is not found in native human antibodies. For example, an Fv can comprise a linker peptide, such as two to about eight glycine or other amino acid residues, which connects the variable region of the heavy chain and the variable region of the light chain. Such linker peptides are considered to be of human origin.

Bispecific, heterospecific, heteroconjugate or similar antibodies can also be used that are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for at least one CNGH0004 polypeptide, the other one is for any other antigen. Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-

expression of two immunoglobulin heavy chain-light chain pairs, where the two heavy chains have different specificities (Milstein and Cuello, Nature 305:537 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed, e.g., in WO 93/08829, US Patent Nos, 6210668, 6193967, 6132992, 6106833, 6060285, 6037453, 6010902, 5989530, 5959084, 5959083, 5932448, 5833985, 5821333, 5807706, 5643759, 5601819, 5582996, 5496549, 4676980, WO 91/00360, WO 92/00373, EP 03089, Traunecker et al., EMBO J. 10:3655 (1991), Suresh et al., Methods in Enzymology 121:210 (1986), each entirely incorporated herein by reference.

Such antibodies optionally further affect a specific ligand, such as but not limited to where such antibody modulates, decreases, increases, antagonizes, angonizes, mitigates, aleviates, blocks, inhibits, abrogates and/or interferes with at least one CNGH0004 activity or binding, or with CNGH0004 receptor activity or binding, *in vitro, in* situ and/or in *vivo*. As a non-limiting example, a suitable CNGH0004 antibody, specified portion or variant of the present invention can bind at least one CNGH0004, or specified portions, variants or domains thereof. A suitable CNGH0004 antibody, specified portion, or variant can also optionally affect at least one of CNGH0004 activity or function, such as but not limited to, RNA, DNA or polypeptide synthesis, CNGH0004 release, CNGH0004 receptor signaling, membrane CNGH0004 cleavage, CNGH0004 activity, CNGH0004 production and/or synthesis.

CNGH0004 antibodies (also termed CNGH0004 antibodies) useful in the methods and compositions of the present invention can optionally be characterized by high affinity binding to CNGH0004 and optionally and preferably having low toxicity. In particular, an antibody, specified fragment or variant of the invention, where the individual components, such as the variable region, constant region and framework, individually and/or collectively, optionally and preferably possess low immunogenicity, is useful in the present invention. The antibodies that can be used in the invention are optionally characterized by their ability to treat patients for extended periods with measurable alleviation of symptoms and low and/or acceptable toxicity. Low or acceptable immunogenicity and/or high affinity, as well as other suitable properties, can contribute to the therapeutic results achieved. "Low immunogenicity" is defined herein as raising significant HAHA, HACA or HAMA responses in less than about 75%, or preferably less than about 50% of the patients treated and/or raising low titres in the patient treated (less than about 300, preferably less than about 100 measured with a double

antigen enzyme immunoassay) (Elliott *et al.*, *Lancet 344*:1125-1127 (1994), entirely incorporated herein by reference).

Utility

CNGH0004 protein is predicted to be an extracellular matrix protein. All CNGH0004 protein domains are characterized as extracellular domains. In addition to normal placenta and fetal tissue development, protein domains that constitute CNGH0004 are probably also involved in tissue remodeling of airway smooth muscle as well as psoriatic epithelium. Based on its domain structure, CNGH0004 may function through mediating adhesion via metal ion-dependent adhesion sites (MIDAS), or via modulating complement control related to immunological responses. As such, CNGH0004 is a potential therapeutic target for treatment of autoimmune or chronic inflammatory diseases including, but not limited to psoriasis or asthma, and different types of cancers.

The isolated nucleic acids of the present invention can be used for production of at least one CNGH0004 antibody or specified variant thereof, which can be used to measure or effect in an cell, tissue, organ or animal (including mammals and humans), to diagnose, monitor, modulate, treat, alleviate, help prevent the incidence of, or reduce the symptoms of, at least one CNGH0004 condition, selected from, but not limited to, at least one of an immune disorder or disease, a cardiovascular disorder or disease, an infectious, malignant, and/or neurologic disorder or disease, or other known or specified CNGH0004 related condition.

Such a method can comprise administering an effective amount of a composition or a pharmaceutical composition comprising at least one CNGH0004 antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment, alleviation, prevention, or reduction in symptoms, effects or mechanisms. The effective amount can comprise an amount of about 0.001 to 500 mg/kg per single (e.g., bolus), multiple or continuous administration, or to achieve a serum concentration of 0.01-5000 μg/ml serum concentration per single, multiple, or continuous administration, or any effective range or value therein, as done and determined using known methods, as described herein or known in the relevant arts.

Citations

All publications or patents cited herein are entirely incorporated herein by reference as they show the state of the art at the time of the present invention and/or to provide description and enablement of the present invention. Publications refer to any scientific or patent publications, or any other information available in any media format, including all recorded, electronic or printed formats. The following references are entirely incorporated herein by reference: Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and

Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Polypeptide Science, John Wiley & Sons, NY, NY, (1997-2001).

Antibodies of the Present Invention.

At least one CNGH0004 antibody of the present invention can be optionally produced by a cell line, a mixed cell line, an immortalized cell or clonal population of immortalized cells, as well known in the art. See, e.g., Ausubel, et al., ed., Current Protocols in Molecular Biology, John Wiley & Sons, Inc., NY, NY (1987-2001); Sambrook, et al., Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor, NY (1989); Harlow and Lane, antibodies, a Laboratory Manual, Cold Spring Harbor, NY (1989); Colligan, et al., eds., Current Protocols in Immunology, John Wiley & Sons, Inc., NY (1994-2001); Colligan et al., Current Protocols in Polypeptide Science, John Wiley & Sons, NY, NY, (1997-2001), each entirely incorporated herein by reference.

Human antibodies that are specific for human CNGH0004 polypeptides or fragments thereof can be raised against an appropriate immunogenic antigen, such as isolated and/or CNGH0004 polypeptide or a portion thereof (including synthetic molecules, such as synthetic peptides). Other specific or general mammalian antibodies can be similarly raised. Preparation of immunogenic antigens, and monoclonal antibody production can be performed using any suitable technique.

In one approach, a hybridoma is produced by fusing a suitable immortal cell line (e.g., a myeloma cell line such as, but not limited to, Sp2/0, Sp2/0-AG14, NSO, NS1, NS2, AE-1, L.5, >243, P3X63Ag8.653, Sp2 SA3, Sp2 MAI, Sp2 SS1, Sp2 SA5, U937, MLA 144, ACT IV, MOLT4, DA-1, JURKAT, WEHI, K-562, COS, RAJI, NIH 3T3, HL-60, MLA 144, NAMAIWA, NEURO 2A, or the like, or heteromylomas, fusion products thereof, or any cell or fusion cell derived therefrom, or any other suitable cell line as known in the art. See, e.g., www.atcc.org, www.lifetech.com., and the like, with antibody producing cells, such as, but not limited to, isolated or cloned spleen, peripheral blood, lymph, tonsil, or other immune or B cell containing cells, or any other cells expressing heavy or light chain constant or variable or framework or CDR sequences, either as endogenous or heterologous nucleic acid, as recombinant or endogenous, viral, bacterial, algal, prokaryotic, amphibian, insect, reptilian, fish, mammalian, rodent, equine, ovine, goat, sheep, primate, eukaryotic, genomic DNA, cDNA, rDNA, mitochondrial DNA or RNA, chloroplast DNA or RNA, hnRNA, mRNA, tRNA, single, double or triple stranded, hybridized, and the like or any combination thereof. See, e.g., Ausubel, supra, and Colligan, Immunology, supra, chapter 2, entirely incorporated herein by reference.

Antibody producing cells can also be obtained from the peripheral blood or, preferably the spleen or lymph nodes, of humans or other suitable animals that have been immunized with the antigen of interest. Any other suitable host cell can also be used for expressing heterologous or endogenous

nucleic acid encoding an antibody, specified fragment or variant thereof, of the present invention. The fused cells (hybridomas) or recombinant cells can be isolated using selective culture conditions or other suitable known methods, and cloned by limiting dilution or cell sorting, or other known methods. Cells which produce antibodies with the desired specificity can be selected by a suitable assay (e.g., ELISA).

Other suitable methods of producing or isolating antibodies of the requisite specificity can be used, including, but not limited to, methods that select recombinant antibody from a peptide or polypeptide library (e.g., but not limited to, a bacteriophage, ribosome, oligonucleotide, RNA, cDNA, or the like, display library; e.g., as available from Cambridge antibody Technologies, Cambridgeshire, UK; MorphoSys, Martinsreid/Planegg, DE; Biovation, Aberdeen, Scotland, UK; BioInvent, Lund, Sweden; Dyax Corp., Enzon, Affymax/Biosite; Xoma, Berkeley, CA; Ixsys. See, e.g., EP 368,684, PCT/GB91/01134; PCT/GB92/01755; PCT/GB92/002240; PCT/GB92/00883; PCT/GB93/00605; US 08/350260(5/12/94); PCT/GB94/01422; PCT/GB94/02662; PCT/GB97/01835; (CAT/MRC); WO90/14443; WO90/14424; WO90/14430; PCT/US94/1234; WO92/18619; WO96/07754; (Scripps); EP 614 989 (MorphoSys); WO95/16027 (BioInvent); WO88/06630; WO90/3809 (Dyax); US 4,704,692 (Enzon); PCT/US91/02989 (Affymax); WO89/06283; EP 371 998; EP 550 400; (Xoma); EP 229 046; PCT/US91/07149 (Ixsys); or stochastically generated peptides or polypeptides - US 5723323, 5763192, 5814476, 5817483, 5824514, 5976862, WO 86/05803, EP 590 689 (Ixsys, now Applied Molecular Evolution (AME), each entirely incorporated herein by reference) or that rely upon immunization of transgenic animals (e.g., SCID mice, Nguyen et al., Microbiol. Immunol. 41:901-907 (1997); Sandhu et al., Crit. Rev. Biotechnol. 16:95-118 (1996); Eren et al., Immunol. 93:154-161 (1998), each entirely incorporated by reference as well as related patents and applications) that are capable of producing a repertoire of human antibodies, as known in the art and/or as described herein. Such techniques, include, but are not limited to, ribosome display (Hanes et al., Proc. Natl. Acad. Sci. USA, 94:4937-4942 (May 1997); Hanes et al., Proc. Natl. Acad. Sci. USA, 95:14130-14135 (Nov. 1998)); single cell antibody producing technologies (e.g., selected lymphocyte antibody method ("SLAM") (US pat. No. 5,627,052, Wen et al., J. Immunol. 17:887-892 (1987); Babcook et al., Proc. Natl. Acad. Sci. USA 93:7843-7848 (1996)); gel microdroplet and flow cytometry (Powell et al., Biotechnol. 8:333-337 (1990); One Cell Systems, Cambridge, MA; Gray et al., J. Imm. Meth. 182:155-163 (1995); Kenny et al., Bio/Technol. 13:787-790 (1995)); B-cell selection (Steenbakkers et al., Molec. Biol. Reports 19:125-134 (1994); Jonak et al., Progress Biotech, Vol. 5, In Vitro Immunization in Hybridoma Technology, Borrebaeck, ed., Elsevier Science Publishers B.V., Amsterdam, Netherlands (1988)).

Methods for engineering or humanizing non-human or human antibodies can also be used and are well known in the art. Generally, a humanized or engineered antibody has one or more amino acid residues from a source which is non-human, e.g., but not limited to mouse, rat, rabbit, non-human primate or other mammal. These human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable, constant or other domain of a known human sequence. Known human Ig sequences are disclosed, e.g., www.ncbi.nlm.nih.gov/entrez/query.fcgi; www.atcc.org/phage/hdb.html; www.sciquest.com/; www.abcam.com/; www.antibodyresource.com/onlinecomp.html; www.public.iastate.edu/~pedro/research_tools.html; www.mgen.uni-heidelberg.de/SD/IT/IT.html; www.whfreeman.com/immunology/CH05/kuby05.htm; www.library.thinkquest.org/12429/Immune/Antibody.html; www.hhmi.org/grants/lectures/1996/vlab/; www.path.cam.ac.uk/~mrc7/mikeimages.html; www.antibodyresource.com/; mcb.harvard.edu/BioLinks/Immunology.html.www.immunologylink.com/; pathbox.wustl.edu/~hcenter/index.html; www.biotech.ufl.edu/~hcl/; www.pebio.com/pa/340913/340913.html; www.nal.usda.gov/awic/pubs/antibody/; www.m.ehime-u.ac.jp/~yasuhito/Elisa.html; www.biodesign.com/table.asp; www.icnet.uk/axp/facs/davies/links.html; www.biotech.ufl.edu/~fccl/protocol.html; www.isac-net.org/sites_geo.html; aximt1.imt.uni-marburg.de/~rek/AEPStart.html; baserv.uci.kun.nl/~jraats/links1.html; www.recab.uni-hd.de/immuno.bme.nwu.edu/; www.mrc-cpe.cam.ac.uk/imt-doc/public/INTRO.html; www.ibt.unam.mx/vir/V_mice.html; imgt.cnusc.fr:8104/; www.biochem.ucl.ac.uk/~martin/abs/index.html; antibody.bath.ac.uk/; abgen.cvm.tamu.edu/lab/wwwabgen.html; www.unizh.ch/~honegger/AHOseminar/Slide01.html; www.cryst.bbk.ac.uk/~ubcg07s/; www.nimr.mrc.ac.uk/CC/ccaewg/ccaewg.htm; www.path.cam.ac.uk/~mrc7/humanisation/TAHHP.html; www.ibt.unam.mx/vir/structure/stat_aim.html; www.biosci.missouri.edu/smithgp/index.html; www.cryst.bioc.cam.ac.uk/~fmolina/Web-pages/Pept/spottech.html; www.jerini.de/fr_products.htm; www.patents.ibm.com/ibm.html.Kabat et al., Sequences of Polypeptides of Immunological Interest, U.S. Dept. Health (1983), each entirely incorporated herein by reference.

Such imported sequences can be used to reduce immunogenicity or reduce, enhance or modify binding, affinity, on-rate, off-rate, avidity, specificity, half-life, or any other suitable characteristic, as known in the art. Generally part or all of the non-human or human CDR sequences are maintained while the non-human sequences of the variable and constant regions are replaced with human or other amino acids. antibodies can also optionally be humanized with retention of high affinity for the antigen and other favorable biological properties. To achieve this goal, humanized antibodies can be

optionally prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, framework residues can be selected and combined from the consensus and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the CDR residues are directly and most substantially involved in influencing antigen binding. Humanization or engineering of antibodies of the present invention can be performed using any known method, such as but not limited to those described in, Winter (Jones et al., Nature 321:522 (1986); Riechmann et al., Nature 332:323 (1988); Verhoeyen et al., Science 239:1534 (1988)), Sims et al., J. Immunol. 151: 2296 (1993); Chothia and Lesk, J. Mol. Biol. 196:901 (1987), Carter et al., Proc. Natl. Acad. Sci. U.S.A. 89:4285 (1992); Presta et al., J. Immunol. 151:2623 (1993), US patent Nos: 5723323, 5976862, 5824514, 5817483, 5814476, 5763192, 5723323, 5,766886, 5714352, 6204023, 6180370, 5693762, 5530101, 5585089, 5225539; 4816567, PCT/: US98/16280, US96/18978, US91/09630, US91/05939, US94/01234, GB89/01334, GB91/01134, GB92/01755; WO90/14443, WO90/14424, WO90/14430, EP 229246, each entirely incorporated herein by reference, included references cited therein.

The CNGH0004 antibody can also be optionally generated by immunization of a transgenic animal (e.g., mouse, rat, hamster, non-human primate, and the like) capable of producing a repertoire of human antibodies, as described herein and/or as known in the art. Cells that produce a human CNGH0004 antibody can be isolated from such animals and immortalized using suitable methods, such as the methods described herein and/or as known in the art.

Transgenic mice that can produce a repertoire of human antibodies that bind to human antigens can be produced by known methods (e.g., but not limited to, U.S. Pat. Nos: 5,770,428, 5,569,825, 5,545,806, 5,625,126, 5,625,825, 5,633,425, 5,661,016 and 5,789,650 issued to Lonberg *et al.*; Jakobovits *et al.* WO 98/50433, Jakobovits *et al.* WO 98/24893, Lonberg *et al.* WO 98/24884, Lonberg *et al.* WO 97/13852, Lonberg *et al.* WO 94/25585, Kucherlapate *et al.* WO 96/34096, Kucherlapate *et al.* EP 0463 151 B1, Kucherlapate *et al.* EP 0710 719 A1, Surani *et al.* US. Pat. No. 5,545,807, Bruggemann *et al.* WO 90/04036, Bruggemann *et al.* EP 0438 474 B1, Lonberg *et al.* EP 0814 259 A2, Lonberg *et al.* GB 2 272 440 A, Lonberg *et al. Nature* 368:856-859 (1994), Taylor *et al., Int. Immunol.*

6(4)579-591 (1994), Green *et al, Nature Genetics* 7:13-21 (1994), Mendez *et al., Nature Genetics* 15:146-156 (1997), Taylor *et al., Nucleic Acids Research* 20(23):6287-6295 (1992), Tuaillon *et al., Proc Natl Acad Sci USA* 90(8)3720-3724 (1993), Lonberg *et al., Int Rev Immunol* 13(1):65-93 (1995) and Fishwald *et al., Nat Biotechnol* 14(7):845-851 (1996), which are each entirely incorporated herein by reference). Generally, these mice comprise at least one transgene comprising DNA from at least one human immunoglobulin locus that is functionally rearranged, or which can undergo functional rearrangement. The endogenous immunoglobulin loci in such mice can be disrupted or deleted to eliminate the capacity of the animal to produce antibodies encoded by endogenous genes.

Screening antibodies for specific binding to similar polypeptides or fragments can be conveniently achieved using peptide display libraries. This method involves the screening of large collections of peptides for individual members having the desired function or structure. antibody screening of peptide display libraries is well known in the art. The displayed peptide sequences can be from 3 to 5000 or more amino acids in length, frequently from 5-100 amino acids long, and often from about 8 to 25 amino acids long. In addition to direct chemical synthetic methods for generating peptide libraries, several recombinant DNA methods have been described. One type involves the display of a peptide sequence on the surface of a bacteriophage or cell. Each bacteriophage or cell contains the nucleotide sequence encoding the particular displayed peptide sequence. Such methods are described in PCT Patent Publication Nos. 91/17271, 91/18980, 91/19818, and 93/08278. Other systems for generating libraries of peptides have aspects of both in vitro chemical synthesis and recombinant methods. See, PCT Patent Publication Nos. 92/05258, 92/14843, and 96/19256. See also, U.S. Patent Nos. 5,658,754; and 5,643,768. Peptide display libraries, vector, and screening kits are commercially available from such suppliers as Invitrogen (Carlsbad, CA), and Cambridge antibody Technologies (Cambridgeshire, UK). See, e.g., U.S. Pat. Nos. 4704692, 4939666, 4946778, 5260203, 5455030, 5518889, 5534621, 5656730, 5763733, 5767260, 5856456, assigned to Enzon; 5223409, 5403484, 5571698, 5837500, assigned to Dyax, 5427908, 5580717, assigned to Affymax; 5885793, assigned to Cambridge antibody Technologies; 5750373, assigned to Genentech, 5618920, 5595898, 5576195, 5698435, 5693493, 5698417, assigned to Xoma, Colligan, supra; Ausubel, *supra*; or Sambrook, *supra,* each of the above patents and publications entirely incorporated herein by reference.

Antibodies of the present invention can also be prepared using at least one CNGH0004 antibody encoding nucleic acid to provide transgenic animals or mammals, such as goats, cows, horses, sheep, and the like, that produce such antibodies in their milk. Such animals can be provided using known methods. See, e.g., but not limited to, US patent nos. 5,827,690; 5,849,992; 4,873,316;

5,849,992; 5,994,616; 5,565,362; 5,304,489, and the like, each of which is entirely incorporated herein by reference.

Antibodies of the present invention can additionally be prepared using at least one CNGH0004 antibody encoding nucleic acid to provide transgenic plants and cultured plant cells (e.g., but not limited to tobacco and maize) that produce such antibodies, specified portions or variants in the plant parts or in cells cultured therefrom. As a non-limiting example, transgenic tobacco leaves expressing recombinant polypeptides have been successfully used to provide large amounts of recombinant polypeptides, e.g., using an inducible promoter. See, e.g., Cramer et al., Curr. Top. Microbol. Immunol. 240:95-118 (1999) and references cited therein. Also, transgenic maize have been used to express mammalian polypeptides at commercial production levels, with biological activities equivalent to those produced in other recombinant systems or purified from natural sources. See, e.g., Hood et al., Adv. Exp. Med. Biol. 464:127-147 (1999) and references cited therein. antibodies have also been produced in large amounts from transgenic plant seeds including antibody fragments, such as single chain antibodies (scFv's), including tobacco seeds and potato tubers. See, e.g., Conrad et al., Plant Mol. Biol. 38:101-109 (1998) and reference cited therein. Thus, antibodies of the present invention can also be produced using transgenic plants, according to know methods. See also, e.g., Fischer et al., Biotechnol. Appl. Biochem. 30:99-108 (Oct., 1999), Ma et al., Trends Biotechnol. 13:522-7 (1995); Ma et al., Plant Physiol. 109:341-6 (1995); Whitelam et al., Biochem. Soc. Trans. 22:940-944 (1994); and references cited therein. Each of the above references is entirely incorporated herein by reference.

The antibodies of the invention can bind human CNGH0004 with a wide range of affinities (K_D). In a preferred embodiment, at least one human mAb of the present invention can optionally bind human CNGH0004 with high affinity. For example, a human mAb can bind human CNGH0004 with a K_D equal to or less than about 10^{-7} M, such as but not limited to, 0.1-9.9 (or any range or value therein) X 10^{-7}, 10^{-8}, 10^{-9},10^{-10}, 10^{-11}, 10^{-12}, 10^{-13} or any range or value therein.

The affinity or avidity of an antibody for an antigen can be determined experimentally using any suitable method. (See, for example, Berzofsky, *et al.*, "Antibody-Antigen Interactions," In *Fundamental Immunology*, Paul, W. E., Ed., Raven Press: New York, NY (1984); Kuby, Janis *Immunology*, W. H. Freeman and Company: New York, NY (1992); and methods described herein). The measured affinity of a particular antibody-antigen interaction can vary if measured under different conditions (e.g., salt concentration, pH). Thus, measurements of affinity and other antigen-binding parameters (e.g., K_D, K_a, K_d) are preferably made with standardized solutions of antibody and antigen, and a standardized buffer, such as the buffer described herein.

Nucleic Acid Molecules

Using the information provided herein, such as the nucleotide sequences encoding at least 70-100% of the contiguous amino acids of at least one of SEQ ID NO:1, specified fragments, variants or consensus sequences thereof, or a deposited vector comprising at least one of these sequences, a nucleic acid molecule of the present invention encoding at least one CNGH0004 antibody can be obtained using methods described herein or as known in the art, such as but not limited to SEQ ID NO:2.

Nucleic acid molecules of the present invention can be in the form of RNA, such as mRNA, hnRNA, tRNA or any other form, or in the form of DNA, including, but not limited to, cDNA and genomic DNA obtained by cloning or produced synthetically, or any combinations thereof. The DNA can be triple-stranded, double-stranded or single-stranded, or any combination thereof. Any portion of at least one strand of the DNA or RNA can be the coding strand, also known as the sense strand, or it can be the non-coding strand, also referred to as theanti-sense strand.

Isolated nucleic acid molecules of the present invention can include nucleic acid molecules comprising an open reading frame (ORF), optionally with one or more introns, e.g., but not limited to, at least one specified portion of at least one CDR, as CDR1, CDR2 and/or CDR3 of at least one heavy chain or light chain; nucleic acid molecules comprising the coding sequence for an CNGH0004 antibody or variable region; and nucleic acid molecules which comprise a nucleotide sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode at least one CNGH0004 antibody as described herein and/or as known in the art. Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate such degenerate nucleic acid variants that code for specific CNGH0004 antibodies of the present invention. See, e.g., Ausubel, et al., *supra*, and such nucleic acid variants are included in the present invention. Non-limiting examples of isolated nucleic acid molecules of the present inveniton include the CDR sequences corresponding to non-limiting examples of a nucleic acid encoding, respectively, HC CDR1, HC CDR2, HC CDR3, LC CDR1, LC CDR2, LC CDR3, HC variable region and LC variable region.

As indicated herein, nucleic acid molecules of the present invention which comprise a nucleic acid encoding a CNGH0004 antibody can include, but are not limited to, those encoding the amino acid sequence of an antibody fragment, by itself; the coding sequence for the entire antibody or a portion thereof; the coding sequence for an antibody, fragment or portion, as well as additional sequences, such as the coding sequence of at least one signal leader or fusion peptide, intron, non-coding 5' and 3' sequences, such as the transcribed, non-translated sequences that play a role in transcription, mRNA processing, including splicing and polyadenylation signals (for example - ribosome binding and

stability of mRNA); an additional coding sequence that codes for additional amino acids, such as those that provide additional functionalities. Thus, the sequence encoding an antibody can be fused to a marker sequence, such as a sequence encoding a peptide that facilitates purification of the fused antibody comprising an antibody fragment or portion.

Polynucleotides Which Selectively Hybridize to a Polynucleotide as Described Herein

The present invention provides isolated nucleic acids that hybridize under selective hybridization conditions to a polynucleotide disclosed herein. Thus, the polynucleotides of this embodiment can be used for isolating, detecting, and/or quantifying nucleic acids comprising such polynucleotides. For example, polynucleotides of the present invention can be used to identify, isolate, or amplify partial or full-length clones in a deposited library. In some embodiments, the polynucleotides are genomic or cDNA sequences isolated, or otherwise complementary to, a cDNA from a human or mammalian nucleic acid library.

Preferably, the cDNA library comprises at least 80% full-length sequences, preferably at least 85% or 90% full-length sequences, and more preferably at least 95% full-length sequences. The cDNA libraries can be normalized to increase the representation of rare sequences. Low or moderate stringency hybridization conditions are typically, but not exclusively, employed with sequences having a reduced sequence identity relative to complementary sequences. Moderate and high stringency conditions can optionally be employed for sequences of greater identity. Low stringency conditions allow selective hybridization of sequences having about 70% sequence identity and can be employed to identify orthologous or paralogous sequences.

Optionally, polynucleotides of this invention will encode at least a portion of an antibody encoded by the polynucleotides described herein. The polynucleotides of this invention embrace nucleic acid sequences that can be employed for selective hybridization to a polynucleotide encoding an antibody of the present invention. See, e.g., Ausubel, supra; Colligan, supra, each entirely incorporated herein by reference.

Construction of Nucleic Acids

The isolated nucleic acids of the present invention can be made using (a) recombinant methods, (b) synthetic techniques, (c) purification techniques, or combinations thereof, as well-known in the art.

The nucleic acids can conveniently comprise sequences in addition to a polynucleotide of the present invention. For example, a multi-cloning site comprising one or more endonuclease restriction sites can be inserted into the nucleic acid to aid in isolation of the polynucleotide. Also, translatable sequences can be inserted to aid in the isolation of the translated polynucleotide of the present invention. For example, a hexa-histidine marker sequence provides a convenient means to purify the polypeptides of

the present invention. The nucleic acid of the present invention - excluding the coding sequence - is optionally a vector, adapter, or linker for cloning and/or expression of a polynucleotide of the present invention.

Additional sequences can be added to such cloning and/or expression sequences to optimize their function in cloning and/or expression, to aid in isolation of the polynucleotide, or to improve the introduction of the polynucleotide into a cell. Use of cloning vectors, expression vectors, adapters, and linkers is well known in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*)

Recombinant Methods for Constructing Nucleic Acids

The isolated nucleic acid compositions of this invention, such as RNA, cDNA, genomic DNA, or any combination thereof, can be obtained from biological sources using any number of cloning methodologies known to those of skill in the art. In some embodiments, oligonucleotide probes that selectively hybridize, under stringent conditions, to the polynucleotides of the present invention are used to identify the desired sequence in a cDNA or genomic DNA library. The isolation of RNA, and construction of cDNA and genomic libraries, is well known to those of ordinary skill in the art. (See, e.g., Ausubel, *supra*; or Sambrook, *supra*)

Nucleic Acid Screening and Isolation Methods

A cDNA or genomic library can be screened using a probe based upon the sequence of a polynucleotide of the present invention, such as those disclosed herein. Probes can be used to hybridize with genomic DNA or cDNA sequences to isolate homologous genes in the same or different organisms. Those of skill in the art will appreciate that various degrees of stringency of hybridization can be employed in the assay; and either the hybridization or the wash medium can be stringent. As the conditions for hybridization become more stringent, there must be a greater degree of complementarity between the probe and the target for duplex formation to occur. The degree of stringency can be controlled by one or more of temperature, ionic strength, pH and the presence of a partially denaturing solvent such as formamide. For example, the stringency of hybridization is conveniently varied by changing the polarity of the reactant solution through, for example, manipulation of the concentration of formamide within the range of 0% to 50%. The degree of complementarity (sequence identity) required for detectable binding will vary in accordance with the stringency of the hybridization medium and/or wash medium. The degree of complementarity will optimally be 100%, or 70-100%, or any range or value therein. However, it should be understood that minor sequence variations in the probes and primers can be compensated for by reducing the stringency of the hybridization and/or wash medium.

Methods of amplification of RNA or DNA are well known in the art and can be used according to the present invention without undue experimentation, based on the teaching and guidance presented herein.

Known methods of DNA or RNA amplification include, but are not limited to, polymerase chain reaction (PCR) and related amplification processes (see, e.g., U.S. Patent Nos. 4,683,195, 4,683,202, 4,800,159, 4,965,188, to Mullis, et al.; 4,795,699 and 4,921,794 to Tabor, et al; 5,142,033 to Innis; 5,122,464 to Wilson, et al.; 5,091,310 to Innis; 5,066,584 to Gyllensten, et al; 4,889,818 to Gelfand, et al; 4,994,370 to Silver, et al; 4,766,067 to Biswas; 4,656,134 to Ringold) and RNA mediated amplification that usesanti-sense RNA to the target sequence as a template for double-stranded DNA synthesis (U.S. Patent No. 5,130,238 to Malek, et al, with the tradename NASBA), the entire contents of which references are incorporated herein by reference. (See, e.g., Ausubel, *supra*; or Sambrook, *supra.*)

For instance, polymerase chain reaction (PCR) technology can be used to amplify the sequences of polynucleotides of the present invention and related genes directly from genomic DNA or cDNA libraries. PCR and other in vitro amplification methods can also be useful, for example, to clone nucleic acid sequences that code for polypeptides to be expressed, to make nucleic acids to use as probes for detecting the presence of the desired mRNA in samples, for nucleic acid sequencing, or for other purposes. Examples of techniques sufficient to direct persons of skill through in vitro amplification methods are found in Berger, supra, Sambrook, supra, and Ausubel, supra, as well as Mullis, et al., U.S. Patent No. 4,683,202 (1987); and Innis, et al., PCR Protocols A Guide to Methods and Applications, Eds., Academic Press Inc., San Diego, CA (1990). Commercially available kits for genomic PCR amplification are known in the art. See, e.g., Advantage-GC Genomic PCR Kit (Clontech). Additionally, e.g., the T4 gene 32 polypeptide (Boehringer Mannheim) can be used to improve yield of long PCR products.

Synthetic Methods for Constructing Nucleic Acids

The isolated nucleic acids of the present invention can also be prepared by direct chemical synthesis by known methods (see, e.g., Ausubel, et al., supra). Chemical synthesis generally produces a single-stranded oligonucleotide, which can be converted into double-stranded DNA by hybridization with a complementary sequence, or by polymerization with a DNA polymerase using the single strand as a template. One of skill in the art will recognize that while chemical synthesis of DNA can be limited to sequences of about 100 or more bases, longer sequences can be obtained by the ligation of shorter sequences.

Recombinant Expression Cassettes

The present invention further provides recombinant expression cassettes comprising a nucleic acid of the present invention. A nucleic acid sequence of the present invention, for example a cDNA or a genomic sequence encoding an antibody of the present invention, can be used to construct a recombinant expression cassette that can be introduced into at least one desired host cell. A recombinant expression cassette will typically comprise a polynucleotide of the present invention operably linked to transcriptional initiation regulatory sequences that will direct the transcription of the polynucleotide in the intended host cell. Both heterologous and non-heterologous (i.e., endogenous) promoters can be employed to direct expression of the nucleic acids of the present invention.

In some embodiments, isolated nucleic acids that serve as promoter, enhancer, or other elements can be introduced in the appropriate position (upstream, downstream or in intron) of a non-heterologous form of a polynucleotide of the present invention so as to up or down regulate expression of a polynucleotide of the present invention. For example, endogenous promoters can be altered *in vivo* or *in vitro* by mutation, deletion and/or substitution.

Vectors And Host Cells

The present invention also relates to vectors that include isolated nucleic acid molecules of the present invention, host cells that are genetically engineered with the recombinant vectors, and the production of at least one CNGH0004 antibody by recombinant techniques, as is well known in the art. See, e.g., Sambrook, et al., supra; Ausubel, et al., supra, each entirely incorporated herein by reference.

The polynucleotides can optionally be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it can be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

The DNA insert should be operatively linked to an appropriate promoter. The expression constructs will further contain sites for transcription initiation, termination and, in the transcribed region, a ribosome binding site for translation. The coding portion of the mature transcripts expressed by the constructs will preferably include a translation initiating at the beginning and a termination codon (e.g., UAA, UGA or UAG) appropriately positioned at the end of the mRNA to be translated, with UAA and UAG preferred for mammalian or eukaryotic cell expression.

Expression vectors will preferably but optionally include at least one selectable marker. Such markers include, e.g., but not limited to, methotrexate (MTX), dihydrofolate reductase (DHFR, US Pat.Nos. 4,399,216; 4,634,665; 4,656,134; 4,956,288; 5,149,636; 5,179,017, ampicillin, neomycin (G418), mycophenolic acid, or glutamine synthetase (GS, US Pat.Nos. 5,122,464; 5,770,359;

5,827,739) resistance for eukaryotic cell culture, and tetracycline or ampicillin resistance genes for culturing in *E. coli* and other bacteria or prokaryotics (the above patents are entirely incorporated hereby by reference). Appropriate culture mediums and conditions for the above-described host cells are known in the art. Suitable vectors will be readily apparent to the skilled artisan. Introduction of a vector construct into a host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection or other known methods. Such methods are described in the art, such as Sambrook, supra, Chapters 1-4 and 16-18; Ausubel, supra, Chapters 1, 9, 13, 15, 16.

At least one antibody of the present invention can be expressed in a modified form, such as a fusion polypeptide, and can include not only secretion signals, but also additional heterologous functional regions. For instance, a region of additional amino acids, particularly charged amino acids, can be added to the N-terminus of an antibody to improve stability and persistence in the host cell, during purification, or during subsequent handling and storage. Also, peptide moieties can be added to an antibody of the present invention to facilitate purification. Such regions can be removed prior to final preparation of an antibody or at least one fragment thereof. Such methods are described in many standard laboratory manuals, such as Sambrook, supra, Chapters 17.29-17.42 and 18.1-18.74; Ausubel, supra, Chapters 16, 17 and 18.

Those of ordinary skill in the art are knowledgeable in the numerous expression systems available for expression of a nucleic acid encoding a polypeptide of the present invention.

Alternatively, nucleic acids of the present invention can be expressed in a host cell by turning on (by manipulation) in a host cell that contains endogenous DNA encoding an antibody of the present invention. Such methods are well known in the art, e.g., as described in US patent Nos. 5,580,734, 5,641,670, 5,733,746, and 5,733,761, entirely incorporated herein by reference.

Illustrative of cell cultures useful for the production of the antibodies, specified portions or variants thereof, are mammalian cells. Mammalian cell systems often will be in the form of monolayers of cells although mammalian cell suspensions or bioreactors can also be used. A number of suitable host cell lines capable of expressing intact glycosylated polypeptides have been developed in the art, and include the COS-1 (e.g., ATCC CRL 1650), COS-7 (e.g., ATCC CRL-1651), HEK293, BHK21 (e.g., ATCC CRL-10), CHO (e.g., ATCC CRL 1610) and BSC-1 (e.g., ATCC CRL-26) cell lines, Cos-7 cells, CHO cells, hep G2 cells, P3X63Ag8.653, SP2/0-Ag14, 293 cells, HeLa cells and the like, which are readily available from, for example, American Type Culture Collection, Manassas, Va (www.atcc.org). Preferred host cells include cells of lymphoid origin such as myeloma and lymphoma cells. Particularly preferred host cells are P3X63Ag8.653 cells (ATCC Accession Number CRL-1580) and

SP2/0-Ag14 cells (ATCC Accession Number CRL-1851). In a particularly preferred embodiment, the recombinant cell is a P3X63Ab8.653 or a SP2/0-Ag14 cell.

Expression vectors for these cells can include one or more of the following expression control sequences, such as, but not limited to an origin of replication; a promoter (e.g., late or early SV40 promoters, the CMV promoter (US Pat.Nos. 5,168,062; 5,385,839), an HSV tk promoter, a pgk (phosphoglycerate kinase) promoter, an EF-1 alpha promoter (US Pat.No. 5,266,491), at least one human immunoglobulin promoter; an enhancer, and/or processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites (e.g., an SV40 large T Ag poly A addition site), and transcriptional terminator sequences. See, e.g., Ausubel et al., supra; Sambrook, et al., supra. Other cells useful for production of nucleic acids or polypeptides of the present invention are known and/or available, for instance, from the American Type Culture Collection Catalogue of Cell Lines and Hybridomas (www.atcc.org) or other known or commercial sources.

When eukaryotic host cells are employed, polyadenlyation or transcription terminator sequences are typically incorporated into the vector. An example of a terminator sequence is the polyadenlyation sequence from the bovine growth hormone gene. Sequences for accurate splicing of the transcript can also be included. An example of a splicing sequence is the VP1 intron from SV40 (Sprague, et al., J. Virol. 45:773-781 (1983)). Additionally, gene sequences to control replication in the host cell can be incorporated into the vector, as known in the art.

Purification of a CNGH0004 Polypeptide or Antibody

A CNGH0004 polypeptide or antibody can be recovered and purified from recombinant cell cultures by well-known methods including, but not limited to, polypeptide A purification, ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. High performance liquid chromatography ("HPLC") can also be employed for purification. See, e.g., Colligan, Current Protocols in Immunology, or Current Protocols in Polypeptide Science, John Wiley & Sons, NY, NY, (1997-2001), e.g., Chapters 1, 4, 6, 8, 9, 10, each entirely incorporated herein by reference.

CNGH0004 polypeptides and antibodies of the present invention include naturally purified products, products of chemical synthetic procedures, and products produced by recombinant techniques from a eukaryotic host, including, for example, yeast, higher plant, insect and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptide or antibody of the present invention can be glycosylated or can be non-glycosylated, with glycosylated preferred. Such methods are described in many standard laboratory manuals, such as Sambrook, supra,

Sections 17.37-17.42; Ausubel, supra, Chapters 10, 12, 13, 16, 18 and 20, Colligan, Protein Science, supra, Chapters 12-14, all entirely incorporated herein by reference.

CNGH0004 Polypeptides and Antibodies

The isolated polypeptides and antibodies of the present invention comprise at least one polypeptide and/or antibody amino acid sequence disclosed or described herein encoded by any suitable polynucleotide, or any at least one isolated or prepared polypeptide antibody. Preferably, the at least one polypeptide has at least one CNGH0004 activity and the at least one antibody binds human CNGH0004 and, thereby partially or substantially modulates at least one structural or biological activity of at least one CNGH0004 polypeptide.

As used herein, the term "CNGH0004 polypeptide" refers to a polypeptide as described herein that has at least one CNGH0004-dependent activity, such as 5-10000%, of the activity of a known or other CNGH0004 polypeptide or active portion thereof, preferably by at least about 10, 20, 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, or 1000% or more, depending on the assay. The capacity of a CNGH0004 polypeptide to have at least one CNGH0004-dependent activity is preferably assessed by at least one suitable CNGH0004 polypeptide or receptor assay, as described herein and/or as known in the art.

As used herein, the term "neutralizing antibody" refers to an antibody that can inhibit at least one CNGH0004-dependent activity by about 5-1020%, preferably by at least about 10, 20, 30, 40, 50, 55, 60, 65, 70, 75, 80, 85, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900, or 1000% or more depending on the assay. The capacity of a CNGH0004 antibody to inhibit an CNGH0004-dependent activity is preferably assessed by at least one suitable CNGH0004 polypeptide or receptor assay, as described herein and/or as known in the art. An antibody of the invention can be of any class (IgG, IgA, IgM, IgE, IgD, etc.) or isotype and can comprise a kappa or lambda light chain. In one embodiment, the human antibody comprises an IgG heavy chain or defined fragment, for example, at least one of isotypes, IgG1, IgG2, IgG3 or IgG4. Antibodies of this type can be prepared by employing a transgenic mouse or other trangenic non-human mammal comprising at least one human light chain (e.g., combination of V, D and J regions) or heavy chain (e.g., γ1, γ2, γ3, γ4, μ1, α1, α2, δ, ε) transgenes as described herein and/or as known in the art. In another embodiment, the human CNGH0004 human antibody comprises an IgG1 heavy chain and an IgG1 light chain.

At least one antibody of the invention binds at least one specified epitope specific to at least one CNGH0004 polypeptide, subunit, fragment, portion or any combination thereof. The at least one epitope can comprise at least one antibody binding region that comprises at least one portion of the polypeptide, which epitope can optionally comprise at least one portion of at least one extracellular,

soluble, hydrophillic, external or cytoplasmic portion of the polypeptide. The at least one specified epitope can comprise any combination of at least one amino acid sequence of at least 1-3 amino acids to the entire specified portion of contiguous amino acids of the SEQ ID NO:1.

The at least one antibody of the present invention can preferably comprise at least one antigen-binding region that comprises at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one heavy chain variable region and/or at least one human complementarity determining region (CDR1, CDR2 and CDR3) or variant of at least one light chain variable region. In a particular embodiment, the polypeptide and antibody can have an antigen-binding region that comprises at least a portion of at least one heavy chain (HC) CDR (i.e., HC CDR1, HC CDR2 and/or HC CDR3) having the amino acid sequence of the corresponding HC CDRs 1, 2 and/or 3. In another particular embodiment, the antibody or antigen-binding portion or variant can have at least one antigen-binding region that comprises at least a portion of at least one light chain (LC) CDR (i.e., LC CDR1, LC CDR2 and/or LC CDR3). Such antibodies can be prepared by chemically joining together the various portions (e.g., CDRs, framework) of the antibody using conventional techniques, by preparing and expressing a (i.e., one or more) nucleic acid molecule that encodes the antibody using conventional techniques of recombinant DNA technology or by using any other suitable method.

The CNGH0004 antibody can comprise at least one of a heavy or light chain variable region having a defined amino acid sequence. For example, in a preferred embodiment, the CNGH0004 antibody comprises at least one heavy chain variable region; and/or at least one light chain variable region. Antibodies that bind to human CNGH0004 and that comprise a defined heavy or light chain variable region can be prepared using suitable methods, such as phage display (Katsube, Y., *et al.*, *Int J Mol. Med*, 1(5):863-868 (1998)) or methods that employ transgenic animals, as known in the art and/or as described herein. For example, a transgenic mouse, comprising a functionally rearranged human immunoglobulin heavy chain transgene and a transgene comprising DNA from a human immunoglobulin light chain locus that can undergo functional rearrangement, can be immunized with human CNGH0004 or a fragment thereof to elicit the production of antibodies. If desired, the antibody producing cells can be isolated and hybridomas or other immortalized antibody-producing cells can be prepared as described herein and/or as known in the art. Alternatively, the antibody, specified portion or variant can be expressed using the encoding nucleic acid or portion thereof in a suitable host cell.

The invention also relates to antibodies, antigen-binding fragments, immunoglobulin chains and CDRs comprising amino acids in a sequence that is substantially the same as an amino acid sequence described herein. Preferably, such antibodies or antigen-binding fragments and antibodies comprising such chains or CDRs can bind human CNGH0004 with high affinity (e.g., K_D less than or

equal to about 10^{-9} M). Amino acid sequences that are substantially the same as the sequences described herein include sequences comprising conservative amino acid substitutions, as well as amino acid deletions and/or insertions. A conservative amino acid substitution refers to the replacement of a first amino acid by a second amino acid that has chemical and/or physical properties (e.g, charge, structure, polarity, hydrophobicity/ hydrophilicity) that are similar to those of the first amino acid. Conservative substitutions include replacement of one amino acid by another within the following groups: lysine (K), arginine (R) and histidine (H); aspartate (D) and glutamate (E); asparagine (N), glutamine (Q), serine (S), threonine (T), tyrosine (Y), K, R, H, D and E; alanine (A), valine (V), leucine (L), isoleucine (I), proline (P), phenylalanine (F), tryptophan (W), methionine (M), cysteine (C) and glycine (G); F, W and Y; C, S and T.

Amino Acid Codes

The amino acids that make up CNGH0004 polypeptides or antibodies of the present invention are often abbreviated. The amino acid designations can be indicated by designating the amino acid by its single letter code, its three letter code, name, or three nucleotide codon(s) as is well understood in the art (see Alberts, B., et al., Molecular Biology of The Cell, Third Ed., Garland Publishing, Inc.,New York, 1994):

SINGLE LETTER CODE	THREE LETTER CODE	NAME	THREE NUCLEOTIDE CODON(S)
A	Ala	Alanine	GCA, GCC, GCG, GCU
C	Cys	Cysteine	UGC, UGU
D	Asp	Aspartic acid	GAC, GAU
E	Glu	Glutamic acid	GAA, GAG
F	Phe	Phenylanine	UUC, UUU
G	Gly	Glycine	GGA, GGC, GGG, GGU
H	His	Histidine	CAC, CAU
I	Ile	Isoleucine	AUA, AUC, AUU
K	Lys	Lysine	AAA, AAG
L	Leu	Leucine	UUA, UUG, CUA, CUC, CUG, CUU
M	Met	Methionine	AUG
N	Asn	Asparagine	AAC, AAU
P	Pro	Proline	CCA, CCC, CCG, CCU
Q	Gln	Glutamine	CAA, CAG
R	Arg	Arginine	AGA, AGG, CGA, CGC, CGG, CGU
S	Ser	Serine	AGC, AGU, UCA, UCC, UCG, UCU
T	Thr	Threonine	ACA, ACC, ACG, ACU
V	Val	Valine	GUA, GUC, GUG, GUU
W	Trp	Tryptophan	UGG

Y	Tyr	Tyrosine	UAC, UAU

An CNGH0004 antibody of the present invention can include one or more amino acid substitutions, deletions or additions, either from natural mutations or human manipulation, as specified herein.

Of course, the number of amino acid substitutions a skilled artisan would make depends on many factors, including those described above. Generally speaking, the number of amino acid substitutions, insertions or deletions for any given CNGH0004 antibody, fragment or variant will not be more than 40, 30, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, such as 1-30 or any range or value therein, as specified herein.

Amino acids in an CNGH0004 antibody of the present invention that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (e.g., Ausubel, supra, Chapters 8, 15; Cunningham and Wells, Science 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity, such as, but not limited to at least one CNGH0004 neutralizing activity. Sites that are critical for antibody binding can also be identified by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith, et al., J. Mol. Biol. 224:899-904 (1992) and de Vos, et al., Science 255:306-312 (1992)).

CNGH0004 polypeptides of the present invention can include, but are not limited to, at least one portion, sequence or combination selected from 3-100 to all of the contiguous amino acids of at least one of SEQ ID NO:1, such as but not limited to, 1-82, 83-259, 259-377, 378-433, 434-438, 438-493, 498-559, 1631-1685, 1690-1743, 1789-1842, 2021-2078, 2083-2141, 2146-2199, 2204-2259, 2264-2318, 2323-2376, 2381-2435, 2440-2493, 2498-2551, 2556-2608, 2660-2712, 2717-2770, 2775-2828, 2833-2886, 2891-2944, 2949-3002, 3007-3059, 3064-3117, 3122-3176, 3181-3236, 3241-3294, 3299-3352, 3357-3411, 3416-3468, 1231-1267, 1269-1305, 1307-1343, 1345-1381, 1383-1419, 1748-1784, 3468-3499, 3504-3531, 3536-3563, 1431-1623, 643-722, 561-642, 1196-1229, 727-787, 1847-1900, 1963-2016, 1905-1958, 999-1036, 1041-1106, 1108-1160, 1-41, or 305-360 of SEQ ID NO:1.

Non-limiting CDRs or portions of CNGH0004 polypeptides or antibodies of the invention that can enhance or maintain at least one of the listed activities include, but are not limited to, any of the above polypeptides, further comprising at least one mutation corresponding to at least one substitution selected from the group consisting of at least one of S249L, V507I, C842W, E980G, Y1063C, K1416Q, D1442V, A1810E.

An CNGH0004 polypeptide can further optionally comprise a polypeptide of at least one of 70-100% of the contiguous amino acids of at least one of SEQ ID NO:1 or any variant thereof.

In one embodiment, the amino acid sequence of a CNGH0004 polypeptide or antibody has about 70-100% identity (e.g., 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) to the amino acid sequence of the corresponding chain of at least one of SEQ ID NO:1. Preferably, 70-100% amino acid identity (i.e., 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100 or any range or value therein) is determined using a suitable computer algorithm, as known in the art.

The polypeptides and antibodies of the present invention, or specified variants thereof, can comprise any number of contiguous amino acid residues from an antibody of the present invention, wherein that number is selected from the group of integers consisting of from 10-100% of the number of contiguous residues in a CNGH0004 polypeptide or antibody. Optionally, this subsequence of contiguous amino acids is at least about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250 or more amino acids in length, or any range or value therein. Further, the number of such subsequences can be any integer selected from the group consisting of from 1 to 20, such as at least 2, 3, 4, or 5.

As those of skill will appreciate, the present invention includes at least one biologically active polypeptide or antibody of the present invention. Biologically active polypeptides or antibodies have a specific activity at least 20%, 30%, or 40%, and preferably at least 50%, 60%, or 70%, and most preferably at least 80%, 90%, or 95%-1000% of that of the native (non-synthetic), endogenous or related and known polypeptide or antibody. Methods of assaying and quantifying measures of enzymatic activity and substrate specificity, are well known to those of skill in the art.

In another aspect, the invention relates to CNGH0004 polypeptides or antibodies of the invention, as described herein, which are modified by the covalent attachment of a moiety. Such modification can produce a CNGH0004 polypeptide or anibody with improved pharmacokinetic properties (e.g., increased *in vivo* serum half-life). The organic moiety can be a linear or branched hydrophilic polymeric group, fatty acid group, or fatty acid ester group. In particular embodiments, the hydrophilic polymeric group can have a molecular weight of about 800 to about 120,000 Daltons and can be a polyalkane glycol (e.g., polyethylene glycol (PEG), polypropylene glycol (PPG)), carbohydrate polymer, amino acid polymer or polyvinyl pyrolidone, and the fatty acid or fatty acid ester group can comprise from about eight to about forty carbon atoms.

The modified polypeptides and antibodies of the invention can comprise one or more organic moieties that are covalently bonded, directly or indirectly, to the antibody or polypeptide. Each

organic moiety that is bonded to the polypeptide or antibody of the invention can independently be a hydrophilic polymeric group, a fatty acid group or a fatty acid ester group. As used herein, the term "fatty acid" encompasses mono-carboxylic acids and di-carboxylic acids. A "hydrophilic polymeric group," as the term is used herein, refers to an organic polymer that is more soluble in water than in octane. For example, polylysine is more soluble in water than in octane. Thus, a CNGH0004 antibody or polypeptide modified by the covalent attachment of polylysine is encompassed by the invention. Hydrophilic polymers suitable for modifying antibodies or polypeptides of the invention can be linear or branched and include, for example, polyalkane glycols (e.g., PEG, monomethoxy-polyethylene glycol (mPEG), PPG and the like), carbohydrates (e.g., dextran, cellulose, oligosaccharides, polysaccharides and the like), polymers of hydrophilic amino acids (e.g., polylysine, polyarginine, polyaspartate and the like), polyalkane oxides (e.g., polyethylene oxide, polypropylene oxide and the like) and polyvinyl pyrolidone. Preferably, the hydrophilic polymer that modifies the polypeptide or antibody of the invention has a molecular weight of about 800 to about 150,000 Daltons as a separate molecular entity. For example PEG_{5000} and $PEG_{20,000}$, wherein the subscript is the average molecular weight of the polymer in Daltons, can be used. The hydrophilic polymeric group can be substituted with one to about six alkyl, fatty acid or fatty acid ester groups. Hydrophilic polymers that are substituted with a fatty acid or fatty acid ester group can be prepared by employing suitable methods. For example, a polymer comprising an amine group can be coupled to a carboxylate of the fatty acid or fatty acid ester, and an activated carboxylate (e.g., activated with N, N-carbonyl diimidazole) on a fatty acid or fatty acid ester can be coupled to a hydroxyl group on a polymer.

Fatty acids and fatty acid esters suitable for modifying antibodies of the invention can be saturated or can contain one or more units of unsaturation. Fatty acids that are suitable for modifying antibodies of the invention include, for example, n-dodecanoate (C_{12}, laurate), n-tetradecanoate (C_{14}, myristate), n-octadecanoate (C_{18}, stearate), n-eicosanoate (C_{20}, arachidate) , n-docosanoate (C_{22}, behenate), n-triacontanoate (C_{30}), n-tetracontanoate (C_{40}), *cis*-Δ9-octadecanoate (C_{18}, oleate), all *cis*-Δ5,8,11,14-eicosatetraenoate (C_{20}, arachidonate), octanedioic acid, tetradecanedioic acid, octadecanedioic acid, docosanedioic acid, and the like. Suitable fatty acid esters include mono-esters of dicarboxylic acids that comprise a linear or branched lower alkyl group. The lower alkyl group can comprise from one to about twelve, preferably one to about six, carbon atoms.

The modified human polypeptides and antibodies can be prepared using suitable methods, such as by reaction with one or more modifying agents. A "modifying agent" as the term is used herein, refers to a suitable organic group (e.g., hydrophilic polymer, a fatty acid, a fatty acid ester) that comprises an activating group. An "activating group" is a chemical moiety or functional group that

can, under appropriate conditions, react with a second chemical group thereby forming a covalent bond between the modifying agent and the second chemical group. For example, amine-reactive activating groups include electrophilic groups such as tosylate, mesylate, halo (chloro, bromo, fluoro, iodo), N-hydroxysuccinimidyl esters (NHS), and the like. Activating groups that can react with thiols include, for example, maleimide, iodoacetyl, acrylolyl, pyridyl disulfides, 5-thiol-2-nitrobenzoic acid thiol (TNB-thiol), and the like. An aldehyde functional group can be coupled to amine- or hydrazide-containing molecules, and an azide group can react with a trivalent phosphorous group to form phosphoramidate or phosphorimide linkages. Suitable methods to introduce activating groups into molecules are known in the art (see for example, Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996)). An activating group can be bonded directly to the organic group (e.g., hydrophilic polymer, fatty acid, fatty acid ester), or through a linker moiety, for example a divalent C_1-C_{12} group wherein one or more carbon atoms can be replaced by a heteroatom such as oxygen, nitrogen or sulfur. Suitable linker moieties include, for example, tetraethylene glycol, $-(CH_2)_3-$, $-NH-(CH_2)_6-NH-$, $-(CH_2)_2-NH-$ and $-CH_2-O-CH_2-CH_2-O-CH_2-CH_2-O-CH-NH-$. Modifying agents that comprise a linker moiety can be produced, for example, by reacting a mono-Boc-alkyldiamine (e.g., mono-Boc-ethylenediamine, mono-Boc-diaminohexane) with a fatty acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) to form an amide bond between the free amine and the fatty acid carboxylate. The Boc protecting group can be removed from the product by treatment with trifluoroacetic acid (TFA) to expose a primary amine that can be coupled to another carboxylate as described, or can be reacted with maleic anhydride and the resulting product cyclized to produce an activated maleimido derivative of the fatty acid. (See, for example, Thompson, *et al.*, WO 92/16221 the entire teachings of which are incorporated herein by reference.)

Modified polypeptides or antibodies of the invention can be produced by reacting the polypeptide or antibody with a modifying agent. For example, the organic moieties can be bonded to the antibody or polypeptide in a non-site specific manner by employing an amine-reactive modifying agent, for example, an NHS ester of PEG. Modified CNGH0004 polypeptides or antibodies can also be prepared by reducing disulfide bonds (e.g., intra-chain disulfide bonds) of the polypeptide and antibody. The reduced polypeptide and antibody can then be reacted with a thiol-reactive modifying agent to produce the modified antibody of the invention. Modified polypeptides and antibodies comprising an organic moiety that is bonded to specific sites of an antibody of the present invention can be prepared using suitable methods, such as reverse proteolysis (Fisch *et al., Bioconjugate Chem.*, 3:147-153 (1992); Werlen *et al., Bioconjugate Chem.*, 5:411-417 (1994); Kumaran *et al., Polypeptide Sci.* 6(10):2233-2241 (1997); Itoh *et al., Bioorg. Chem.*, 24(1): 59-68 (1996); Capellas *et al.*,

Biotechnol. Bioeng., 56(4):456-463 (1997)), and the methods described in Hermanson, G. T., *Bioconjugate Techniques*, Academic Press: San Diego, CA (1996).

ANTI-IDIOTYPE ANTIBODIES TO ANTI-CNGH0004 ANTIBODY COMPOSITIONS

In addition to monoclonal or chimeric CNGH0004 antibodies, the present invention is also directed to an idiotypic (Id) antibody specific for such antibodies of the invention. An anti-Id antibody is an antibody that recognizes unique determinants generally associated with the antigen-binding region of another antibody. The Id can be prepared by immunizing an animal of the same species and genetic type (e.g. mouse strain) as the source of the Id antibody with the antibody or a CDR containing region thereof. The immunized animal will recognize and respond to the idiotypic determinants of the immunizing antibody and produce an anti-Id antibody. The anti-Id antibody may also be used as an "immunogen" to induce an immune response in yet another animal, producing a so-called anti-Id antibody.

CNGH0004 POLYPEPTIDE AND ANTIBODY COMPOSITIONS

The present invention also provides at least one CNGH0004 antibody or polypeptide composition comprising at least one, at least two, at least three, at least four, at least five, or at least 6-50, or any range or value therein, CNGH0004 antibodies or polypeptides thereof, as described herein. Such compositions can comprise 0.00001-99.9999 percent by weight, volume, concentration, molarity, or molality as liquid, gas, or dry solutions, mixtures, suspension, emulsions or colloids, as known in the art or as described herein, on any range or value therein, such as but not limited to 0.00001, 0.00003, 0.00005, 0.00009, 0.0001, 0.0003, 0.0005, 0.0009, 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4., 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 99.1, 99.2, 99.3, 99.4, 99.5, 99.6, 99.7, 99.8, 99.9 %. Such compositions of the present invention thus include but are not limited to 0.00001-100 mg/ml and/or 0.00001-100 mg/g.

The composition can optionally further comprise an effective amount of at least one compound or protein selected from at least one of an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplactic, an immunomodulation drug, an ophthalmic, otic or nasal drug, a topical drug, a nutritional drug or the like. Such drugs are well known in the art, including

formulations, indications, dosing and administration for each presented herein (see., e.g., Nursing 2001 Handbook of Drugs, 21st edition, Springhouse Corp., Springhouse, PA, 2001; Health Professional's Drug Guide 2001, ed., Shannon, Wilson, Stang, Prentice-Hall, Inc, Upper Saddle River, NJ; Pharmcotherapy Handbook, Wells et al., ed., Appleton & Lange, Stamford, CT, each entirely incorporated herein by reference).

The anti-infective drug can be at least one selected from amebicides or at least one antiprotozoals, anthelmintics, antifungals, antimalarials, antituberculotics or at least one antileprotics, aminoglycosides, penicillins, cephalosporins, tetracyclines, sulfonamides, fluoroquinolones, antivirals, macrolide anti-infectives, miscellaneous anti-infectives. The CV drug can be at least one selected from inotropics, antiarrhythmics, antianginals, antihypertensives, antilipemics, miscellaneous cardiovascular drugs. The CNS drug can be at least one selected from nonnarcotic analgesics or at least one selected from antipyretics, nonsteroidal anti-inflammatory drugs, narcotic or at least one opiod analgesics, sedative-hypnotics, anticonvulsants, antidepressants, antianxiety drugs, antipsychotics, central nervous system stimulants, antiparkinsonians, miscellaneous central nervous system drugs. The ANS drug can be at least one selected from cholinergics (parasympathomimetics), anticholinergics, adrenergics (sympathomimetics), adrenergic blockers (sympatholytics), skeletal muscle relaxants, neuromuscular blockers. The respiratory tract drug can be at least one selected from antihistamines, bronchodilators, expectorants or at least one antitussives, miscellaneous respiratory drugs. The GI tract drug can be at least one selected from antacids or at least one adsorbents or at least one antiflatulents, digestive enzymes or at least one gallstone solubilizers, antidiarrheals, laxatives, antiemetics, antiulcer drugs. The hormonal drug can be at least one selected from corticosteroids, androgens or at least one anabolic steroids, estrogens or at least one progestins, gonadotropins, antidiabetic drugs or at least one glucagon, thyroid hormones, thyroid hormone antagonists, pituitary hormones, parathyroid-like drugs. The drug for fluid and electrolyte balance can be at least one selected from diuretics, electrolytes or at least one replacement solutions, acidifiers or at least one alkalinizers. The hematologic drug can be at least one selected from hematinics, anticoagulants, blood derivatives, thrombolytic enzymes. The antineoplastics can be at least one selected from alkylating drugs, antimetabolites, antibiotic antineoplastics, antineoplastics that alter hormone balance, miscellaneous antineoplastics. The immunomodulation drug can be at least one selected from immunosuppressants, vaccines or at least one toxoids, antitoxins or at least one antivenins, immune serums, biological response modifiers. The ophthalmic, otic, and nasal drugs can be at least one selected from ophthalmic anti-infectives, ophthalmic anti-inflammatories, miotics, mydriatics, ophthalmic vasoconstrictors, miscellaneous ophthalmics, otics, nasal drugs. The topical drug can be at least one selected from local anti-infectives,

scabicides or at least one pediculicides, topical corticosteroids. The nutritional drug can be at least one selected from vitamins, minerals, or calorics. See, e.g., contents *of Nursing 2001 Drug Handbook, supra.*

The at least one amebicide or antiprotozoal can be at least one selected from atovaquone, chloroquine hydrochloride, chloroquine phosphate, metronidazole, metronidazole hydrochloride, pentamidine isethionate. The at least one anthelmintic can be at least one selected from mebendazole, pyrantel pamoate, thiabendazole. The at least one antifungal can be at least one selected from amphotericin B, amphotericin B cholesteryl sulfate complex, amphotericin B lipid complex, amphotericin B liposomal, fluconazole, flucytosine, griseofulvin microsize, griseofulvin ultramicrosize, itraconazole, ketoconazole, nystatin, terbinafine hydrochloride. The at least one antimalarial can be at least one selected from chloroquine hydrochloride, chloroquine phosphate, doxycycline, hydroxychloroquine sulfate, mefloquine hydrochloride, primaquine phosphate, pyrimethamine, pyrimethamine with sulfadoxine. The at least one antituberculotic or antileprotic can be at least one selected from clofazimine, cycloserine, dapsone, ethambutol hydrochloride, isoniazid, pyrazinamide, rifabutin, rifampin, rifapentine, streptomycin sulfate. The at least one aminoglycoside can be at least one selected from amikacin sulfate, gentamicin sulfate, neomycin sulfate, streptomycin sulfate, tobramycin sulfate. The at least one penicillin can be at least one selected from amoxcillin/clavulanate potassium, amoxicillin trihydrate, ampicillin, ampicillin sodium, ampicillin trihydrate, ampicillin sodium/sulbactam sodium, cloxacillin sodium, dicloxacillin sodium, mezlocillin sodium, nafcillin sodium, oxacillin sodium, penicillin G benzathine, penicillin G potassium, penicillin G procaine, penicillin G sodium, penicillin V potassium, piperacillin sodium, piperacillin sodium/tazobactam sodium, ticarcillin disodium, ticarcillin disodium/clavulanate potassium. The at least one cephalosporin can be at least one selected from at least one of cefaclor, cefadroxil, cefazolin sodium, cefdinir, cefepime hydrochloride, cefixime, cefmetazole sodium, cefonicid sodium, cefoperazone sodium, cefotaxime sodium, cefotetan disodium, cefoxitin sodium, cefpodoxime proxetil, cefprozil, ceftazidime, ceftibuten, ceftizoxime sodium, ceftriaxone sodium, cefuroxime axetil, cefuroxime sodium, cephalexin hydrochloride, cephalexin monohydrate, cephradine, loracarbef. The at least one tetracycline can be at least one selected from demeclocycline hydrochloride, doxycycline calcium, doxycycline hyclate, doxycycline hydrochloride, doxycycline monohydrate, minocycline hydrochloride, tetracycline hydrochloride. The at least one sulfonamide can be at least one selected from co-trimoxazole, sulfadiazine, sulfamethoxazole, sulfisoxazole, sulfisoxazole acetyl. The at least one fluoroquinolone can be at least one selected from alatrofloxacin mesylate, ciprofloxacin, enoxacin, levofloxacin, lomefloxacin hydrochloride, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin,

trovafloxacin mesylate. The at least one fluoroquinolone can be at least one selected from alatrofloxacin mesylate, ciprofloxacin, enoxacin, levofloxacin, lomefloxacin hydrochloride, nalidixic acid, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin mesylate. The at least one antiviral can be at least one selected from abacavir sulfate, acyclovir sodium, amantadine hydrochloride, amprenavir, cidofovir, delavirdine mesylate, didanosine, efavirenz, famciclovir, fomivirsen sodium, foscarnet sodium, ganciclovir, indinavir sulfate, lamivudine, lamivudine/zidovudine, nelfinavir mesylate, nevirapine, oseltamivir phosphate, ribavirin, rimantadine hydrochloride, ritonavir, saquinavir, saquinavir mesylate, stavudine, valacyclovir hydrochloride, zalcitabine, zanamivir, zidovudine. The at least one macroline anti-infective can be at least one selected from azithromycin, clarithromycin, dirithromycin, erythromycin base, erythromycin estolate, erythromycin ethylsuccinate, erythromycin lactobionate, erythromycin stearate. The at least one miscellaneous anti-infective can be at least one selected from aztreonam, bacitracin, chloramphenicol sodium sucinate, clindamycin hydrochloride, clindamycin palmitate hydrochloride, clindamycin phosphate, imipenem and cilastatin sodium, meropenem, nitrofurantoin macrocrystals, nitrofurantoin microcrystals, quinupristin/dalfopristin, spectinomycin hydrochloride, trimethoprim, vancomycin hydrochloride. (See, e.g., pp. 24-214 of *Nursing 2001 Drug Handbook.*)

The at least one inotropic can be at least one selected from amrinone lactate, digoxin, milrinone lactate. The at least one antiarrhythmic can be at least one selected from adenosine, amiodarone hydrochloride, atropine sulfate, bretylium tosylate, diltiazem hydrochloride, disopyramide, disopyramide phosphate, esmolol hydrochloride, flecainide acetate, ibutilide fumarate, lidocaine hydrochloride, mexiletine hydrochloride, moricizine hydrochloride, phenytoin, phenytoin sodium, procainamide hydrochloride, propafenone hydrochloride, propranolol hydrochloride, quinidine bisulfate, quinidine gluconate, quinidine polygalacturonate, quinidine sulfate, sotalol, tocainide hydrochloride, verapamil hydrochloride. The at least one antianginal can be at least one selected from amlodipidine besylate, amyl nitrite, bepridil hydrochloride, diltiazem hydrochloride, isosorbide dinitrate, isosorbide mononitrate, nadolol, nicardipine hydrochloride, nifedipine, nitroglycerin, propranolol hydrochloride, verapamil, verapamil hydrochloride. The at least one antihypertensive can be at least one selected from acebutolol hydrochloride, amlodipine besylate, atenolol, benazepril hydrochloride, betaxolol hydrochloride, bisoprolol fumarate, candesartan cilexetil, captopril, carteolol hydrochloride, carvedilol, clonidine, clonidine hydrochloride, diazoxide, diltiazem hydrochloride, doxazosin mesylate, enalaprilat, enalapril maleate, eprosartan mesylate, felodipine, fenoldopam mesylate, fosinopril sodium, guanabenz acetate, guanadrel sulfate, guanfacine hydrochloride, hydralazine hydrochloride, irbesartan, isradipine, labetalol hydrchloride, lisinopril, losartan potassium,

methyldopa, methyldopate hydrochloride, metoprolol succinate, metoprolol tartrate, minoxidil, moexipril hydrochloride, nadolol, nicardipine hydrochloride, nifedipine, nisoldipine, nitroprusside sodium, penbutolol sulfate, perindopril erbumine, phentolamine mesylate, pindolol, prazosin hydrochloride, propranolol hydrochloride, quinapril hydrochloride, ramipril, telmisartan, terazosin hydrochloride, timolol maleate, trandolapril, valsartan, verapamil hydrochloride The at least one antilipemic can be at least one selected from atorvastatin calcium, cerivastatin sodium, cholestyramine, colestipol hydrochloride, fenofibrate (micronized), fluvastatin sodium, gemfibrozil, lovastatin, niacin, pravastatin sodium, simvastatin. The at least one miscellaneous CV drug can be at least one selected from abciximab, alprostadil, arbutamine hydrochloride, cilostazol, clopidogrel bisulfate, dipyridamole, eptifibatide, midodrine hydrochloride, pentoxifylline, ticlopidine hydrochloride, tirofiban hydrochloride. (See, e.g., pp. 215-336 of *Nursing 2001 Drug Handbook.*)

The at least one nonnarcotic analgesic or antipyretic can be at least one selected from acetaminophen, aspirin, choline magnesium trisalicylate, diflunisal, magnesium salicylate. The at least one nonsteroidal anti-inflammatory drug can be at least one selected from celecoxib, diclofenac potassium, diclofenac sodium, etodolac, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, indomethacin sodium trihydrate, ketoprofen, ketorolac tromethamine, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, rofecoxib, sulindac. The at least one narcotic or opiod analgesic can be at least one selected from alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, codeine phosphate, codeine sulfate, fentanyl citrate, fentanyl transdermal system, fentanyl transmucosal, hydromorphone hydrochloride, meperidine hydrochloride, methadone hydrochloride, morphine hydrochloride, morphine sulfate, morphine tartrate, nalbuphine hydrochloride, oxycodone hydrochloride, oxycodone pectinate, oxymorphone hydrochloride, pentazocine hydrochloride, pentazocine hydrochloride and naloxone hydrochloride, pentazocine lactate, propoxyphene hydrochloride, propoxyphene napsylate, remifentanil hydrochloride, sufentanil citrate, tramadol hydrochloride. The at least one sedative-hypnotic can be at least one selected from chloral hydrate, estazolam, flurazepam hydrochloride, pentobarbital, pentobarbital sodium, phenobarbital sodium, secobarbital sodium, temazepam, triazolam, zaleplon, zolpidem tartrate. The at least one anticonvulsant can be at least one selected from acetazolamide sodium, carbamazepine, clonazepam, clorazepate dipotassium, diazepam, divalproex sodium, ethosuximde, fosphenytoin sodium, gabapentin, lamotrigine, magnesium sulfate, phenobarbital, phenobarbital sodium, phenytoin, phenytoin sodium, phenytoin sodium (extended), primidone, tiagabine hydrochloride, topiramate, valproate sodium, valproic acid. The at least one antidepressant can be at least one selected from amitriptyline hydrochloride, amitriptyline pamoate, amoxapine, bupropion hydrochloride, citalopram

hydrobromide, clomipramine hydrochloride, desipramine hydrochloride, doxepin hydrochloride, fluoxetine hydrochloride, imipramine hydrochloride, imipramine pamoate, mirtazapine, nefazodone hydrochloride, nortriptyline hydrochloride, paroxetine hydrochloride, phenelzine sulfate, sertraline hydrochloride, tranylcypromine sulfate, trimipramine maleate, venlafaxine hydrochloride. The at least one antianxiety drug can be at least one selected from alprazolam, buspirone hydrochloride, chlordiazepoxide, chlordiazepoxide hydrochloride, clorazepate dipotassium, diazepam, doxepin hydrochloride, hydroxyzine embonate, hydroxyzine hydrochloride, hydroxyzine pamoate, lorazepam, mephrobamate, midazolam hydrochloride, oxazepam. The at least one antipsychotic drug can be at least one selected from chlorpromazine hydrochloride, clozapine, fluphenazine decanoate, fluephenazine enanthate, fluphenazine hydrochloride, haloperidol, haloperidol decanoate, haloperidol lactate, loxapine hydrochloride, loxapine succinate, mesoridazine besylate, molindone hydrochloride, olanzapine, perphenazine, pimozide, prochlorperazine, quetiapine fumarate, risperidone, thioridazine hydrochloride, thiothixene, thiothixene hydrochloride, trifluoperazine hydrochloride. The at least one central nervous system stimulant can be at least one selected from amphetamine sulfate, caffeine, dextroamphetamine sulfate, doxapram hydrochloride, methamphetamine hydrochloride, methylphenidate hydrochloride, modafinil, pemoline, phentermine hydrochloride. The at least one antiparkinsonian can be at least one selected from amantadine hydrochloride, benztropine mesylate, biperiden hydrochloride, biperiden lactate, bromocriptine mesylate, carbidopa-levodopa, entacapone, levodopa, pergolide mesylate, pramipexole dihydrochloride, ropinirole hydrochloride, selegiline hydrochloride, tolcapone, trihexyphenidyl hydrochloride. The at least one miscellaneous central nervous system drug can be at least one selected from bupropion hydrochloride, donepezil hydrochloride, droperidol, fluvoxamine maleate, lithium carbonate, lithium citrate, naratriptan hydrochloride, nicotine polacrilex, nicotine transdermal system, propofol, rizatriptan benzoate, sibutramine hydrochloride monohydrate, sumatriptan succinate, tacrine hydrochloride, zolmitriptan. (See, e.g., pp. 337-530 of *Nursing 2001 Drug Handbook*.)

The at least one cholinergic (e.g., parasymathomimetic) can be at least one selected from bethanechol chloride, edrophonium chloride, neostigmine bromide, neostigmine methylsulfate, physostigmine salicylate, pyridostigmine bromide. The at least one anticholinergics can be at least one selected from atropine sulfate, dicyclomine hydrochloride, glycopyrrolate, hyoscyamine, hyoscyamine sulfate, propantheline bromide, scopolamine, scopolamine butylbromide, scopolamine hydrobromide. The at least one adrenergics (sympathomimetics) can be at least one selected from dobutamine hydrochloride, dopamine hydrochloride, metaraminol bitartrate, norepinephrine bitartrate, phenylephrine hydrochloride, pseudoephedrine hydrochloride, pseudoephedrine sulfate. The at least

one adrenergic blocker (sympatholytic) can be at least one selected from dihydroergotamine mesylate, ergotamine tartrate, methysergide maleate, propranolol hydrochloride. The at least one skeletal muscle relaxant can be at least one selected from baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine hydrochloride, dantrolene sodium, methocarbamol, tizanidine hydrochloride. The at least one neuromuscular blockers can be at least one selected from atracurium besylate, cisatracurium besylate, doxacurium chloride, mivacurium chloride, pancuronium bromide, pipecuronium bromide, rapacuronium bromide, rocuronium bromide, succinylcholine chloride, tubocurarine chloride, vecuronium bromide. (See, e.g., pp. 531-84 of *Nursing 2001 Drug Handbook.*)

The at least one antihistamine can be at least one selected from brompheniramine maleate, cetirizine hydrochloride, chlorpheniramine maleate, clemastine fumarate, cyproheptadine hydrochloride, diphenhydramine hydrochloride, fexofenadine hydrochloride, loratadine, promethazine hydrochloride, promethazine theoclate, triprolidine hydrochloride. The at least one bronchodilators can be at least one selected from albuterol, albuterol sulfate, aminophylline, atropine sulfate, ephedrine sulfate, epinephrine, epinephrine bitartrate, epinephrine hydrochloride, ipratropium bromide, isoproterenol, isoproterenol hydrochloride, isoproterenol sulfate, levalbuterol hydrochloride, metaproterenol sulfate, oxtriphylline, pirbuterol acetate, salmeterol xinafoate, terbutaline sulfate, theophylline. The at least one expectorants or antitussives can be at least one selected from benzonatate, codeine phosphate, codeine sulfate, dextramethorphan hydrobromide, diphenhydramine hydrochloride, guaifenesin, hydromorphone hydrochloride. The at least one miscellaneous respiratory drug can be at least one selected from acetylcysteine, beclomethasone dipropionate, beractant, budesonide, calfactant, cromolyn sodium, dornase alfa, epoprostenol sodium, flunisolide, fluticasone propionate, montelukast sodium, nedocromil sodium, palivizumab, triamcinolone acetonide, zafirlukast, zileuton. (See, e.g., pp. 585-642 of *Nursing 2001 Drug Handbook.*)

The at least one antacid, adsorbents, or antiflatulents can be at least one selected from aluminum carbonate, aluminum hydroxide, calcium carbonate, magaldrate, magnesium hydroxide, magnesium oxide, simethicone, sodium bicarbonate. The at least one digestive enymes or gallstone solubilizers can be at least one selected from pancreatin, pancrelipase, ursodiol. The at least one antidiarrheal can be at least one selected from attapulgite, bismuth subsalicylate, calcium polycarbophil, diphenoxylate hydrochloride or atropine sulfate, loperamide, octreotide acetate, opium tincture, opium tincure (camphorated). The at least one laxative can be at least one selected from bisocodyl, calcium polycarbophil, cascara sagrada, cascara sagrada aromatic fluidextract, cascara sagrada fluidextract, castor oil, docusate calcium, docusate sodium, glycerin, lactulose, magnesium citrate, magnesium hydroxide, magnesium sulfate, methylcellulose, mineral oil, polyethylene glycol or

electrolyte solution, psyllium, senna, sodium phosphates. The at least one antiemetic can be at least one selected from chlorpromazine hydrochloride, dimenhydrinate, dolasetron mesylate, dronabinol, granisetron hydrochloride, meclizine hydrochloride, metoclopramide hydrochloride, ondansetron hydrochloride, perphenazine, prochlorperazine, prochlorperazine edisylate, prochlorperazine maleate, promethazine hydrochloride, scopolamine, thiethylperazine maleate, trimethobenzamide hydrochloride. The at least one antiulcer drug can be at least one selected from cimetidine, cimetidine hydrochloride, famotidine, lansoprazole, misoprostol, nizatidine, omeprazole, rabeprozole sodium, rantidine bismuth citrate, ranitidine hydrochloride, sucralfate. (See, e.g., pp. 643-95 of *Nursing 2001 Drug Handbook.*)

The at least one coricosteroids can be at least one selected from betamethasone, betamethasone acetate or betamethasone sodium phosphate, betamethasone sodium phosphate, cortisone acetate, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, fludrocortisone acetate, hydrocortisone, hydrocortisone acetate, hydrocortisone cypionate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, methylprednisolone, methylprednisolone acetate, methylprednisolone sodium succinate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebutate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate. The at least one androgen or anabolic steroids can be at least one selected from danazol, fluoxymesterone, methyltestosterone, nandrolone decanoate, nandrolone phenpropionate, testosterone, testosterone cypionate, testosterone enanthate, testosterone propionate, testosterone transdermal system. The at least one estrogen or progestin can be at least one selected from esterified estrogens, estradiol, estradiol cypionate, estradiol/norethindrone acetate transdermal system, estradiol valerate, estrogens (conjugated), estropipate, ethinyl estradiol, ethinyl estradiol and desogestrel, ethinyl estradiol and ethynodiol diacetate, ethinyl estradiol and desogestrel, ethinyl estradiol and ethynodiol diacetate, ethinyl estradiol and levonorgestrel, ethinyl estradiol and norethindrone, ethinyl estradiol and norethindrone acetate, ethinyl estradiol and norgestimate, ethinyl estradiol and norgestrel, ethinyl estradiol and norethindrone and acetate and ferrous fumarate, levonorgestrel, medroxyprogesterone acetate, mestranol and norethindron, norethindrone, norethindrone acetate, norgestrel, progesterone. The at least one gonadroptropin can be at least one selected from ganirelix acetate, gonadoreline acetate, histrelin acetate, menotropins. The at least one antidiabetic or glucaon can be at least one selected from acarbose, chlorpropamide, glimepiride, glipizide, glucagon, glyburide, insulins, metformin hydrochloride, miglitol, pioglitazone hydrochloride, repaglinide, rosiglitazone maleate, troglitazone. The at least one thyroid hormone can be at least one selected from levothyroxine sodium, liothyronine sodium, liotrix, thyroid. The at least one thyroid hormone antagonist can be at least one

selected from methimazole, potassium iodide, potassium iodide (saturated solution), propylthiouracil, radioactive iodine (sodium iodide ^{131}I), strong iodine solution. The at least one pituitary hormone can be at least one selected from corticotropin, cosyntropin, desmophressin acetate, leuprolide acetate, repository corticotropin, somatrem, somatropin, vasopressin. The at least one parathyroid-like drug can be at least one selected from calcifediol, calcitonin (human), calcitonin (salmon), calcitriol, dihydrotachysterol, etidronate disodium. (See, e.g., pp. 696-796 of *Nursing 2001 Drug Handbook.*)

The at least one diuretic can be at least one selected from acetazolamide, acetazolamide sodium, amiloride hydrochloride, bumetanide, chlorthalidone, ethacrynate sodium, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, mannitol, metolazone, spironolactone, torsemide, triamterene, urea. The at least one electrolyte or replacement solution can be at least one selected from calcium acetate, calcium carbonate, calcium chloride, calcium citrate, calcium glubionate, calcium gluceptate, calcium gluconate, calcium lactate, calcium phosphate (dibasic), calcium phosphate (tribasic), dextran (high-molecular-weight), dextran (low-molecular-weight), hetastarch, magnesium chloride, magnesium sulfate, potassium acetate, potassium bicarbonate, potassium chloride, potassium gluconate, Ringer's injection, Ringer's injection (lactated), sodium chloride. The at least one acidifier or alkalinizer can be at least one selected from sodium bicarbonate, sodium lactate, tromethamine. (See, e.g., pp. 797-833 of *Nursing 2001 Drug Handbook.*)

The at least one hematinic can be at least one selected from ferrous fumarate, ferrous gluconate, ferrous sulfate, ferrous sulfate (dried), iron dextran, iron sorbitol, polysaccharide-iron complex, sodium ferric gluconate complex. The at least one anticoagulant can be at least one selected from ardeparin sodium, dalteparin sodium, danaparoid sodium, enoxaparin sodium, heparin calcium, heparin sodium, warfarin sodium. The at least one blood derivative can be at least one selected from albumin 5%, albumin 25%, antihemophilic factor, anti-inhibitor coagulant complex, antithrombin III (human), factor IX (human), factor IX complex, plasma protein fractions. The at least one thrombolytic enzyme can be at least one selected from alteplase, anistreplase, reteplase (recombinant), streptokinase, urokinase. (See, e.g., pp. 834-66 of *Nursing 2001 Drug Handbook.*)

The at least one alkylating drug can be at least one selected from busulfan, carboplatin, carmustine, chlorambucil, cisplatin, cyclophosphamide, ifosfamide, lomustine, mechlorethamine hydrochloride, melphalan, melphalan hydrochloride, streptozocin, temozolomide, thiotepa. The at least one antimetabolite can be at least one selected from capecitabine, cladribine, cytarabine, floxuridine, fludarabine phosphate, fluorouracil, hydroxyurea, mercaptopurine, methotrexate, methotrexate sodium, thioguanine. The at least one antibiotic antineoplastic can be at least one selected from bleomycin sulfate, dactinomycin, daunorubicin citrate liposomal, daunorubicin hydrochloride, doxorubicin

hydrochloride, doxorubicin hydrochloride liposomal, epirubicin hydrochloride, idarubicin hydrochloride, mitomycin, pentostatin, plicamycin, valrubicin. The at least one antineoplastics that alter hormone balance can be at least one selected from anastrozole, bicalutamide, estramustine phosphate sodium, exemestane, flutamide, goserelin acetate, letrozole, leuprolide acetate, megestrol acetate, nilutamide, tamoxifen citrate, testolactone, toremifene citrate. The at least one miscellaneous antineoplastic can be at least one selected from asparaginase, bacillus Calmette-Guerin (BCG) (live intravesical), dacarbazine, docetaxel, etoposide, etoposide phosphate, gemcitabine hydrochloride, irinotecan hydrochloride, mitotane, mitoxantrone hydrochloride, paclitaxel, pegaspargase, porfimer sodium, procarbazine hydrochloride, rituximab, teniposide, topotecan hydrochloride, trastuzumab, tretinoin, vinblastine sulfate, vincristine sulfate, vinorelbine tartrate. (See, e.g., pp. 867-963 of *Nursing 2001 Drug Handbook*.)

The at least one immunosuppressant can be at least one selected from azathioprine, basiliximab, cyclosporine, daclizumab, lymphocyte immune globulin, muromonab-CD3, mycophenolate mofetil, mycophenolate mofetil hydrochloride, sirolimus, tacrolimus. The at least one vaccine or toxoid can be at least one selected from BCG vaccine, cholera vaccine, diphtheria and tetanus toxoids (adsorbed), diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed, diphtheria and tetanus toxoids and whole-cell pertussis vaccine, *Haemophilius* b conjugate vaccines, hepatitis A vaccine (inactivated), hepatisis B vaccine (recombinant), influenza virus vaccine 1999-2000 trivalent types A & B (purified surface antigen), influenza virus vaccine 1999-2000 trivalent types A & B (subvirion or purified subvirion), influenza virus vaccine 1999-2000 trivalent types A & B (whole virion), Japanese encephalitis virus vaccine (inactivated), Lyme disease vaccine (recombinant OspA), measles and mumps and rubella virus vaccine (live), measles and mumps and rubella virus vaccine (live attenuated), measles virus vaccine (live attenuated), meningococcal polysaccharide vaccine, mumps virus vaccine (live), plague vaccine, pneumococcal vaccine (polyvalent), poliovirus vaccine (inactivated), poliovirus vaccine (live, oral, trivalent), rabies vaccine (adsorbed), rabies vaccine (human diploid cell), rubella and mumps virus vaccine (live), rubella virus vaccine (live, attenuated), tetanus toxoid (adsorbed), tetanus toxoid (fluid), typhoid vaccine (oral), typhoid vaccine (parenteral), typhoid Vi polysaccharide vaccine, varicella virus vaccine, yellow fever vaccine. The at least one antitoxin or antivenin can be at least one selected from black widow spider antivenin, Crotalidae antivenom (polyvalent), diphtheria antitoxin (equine), *Micrurus fulvius* antivenin). The at least one immune serum can be at least one selected from cytomegalovirus immune globulin (intraveneous), hepatitis B immune globulin (human), immune globulin intramuscular, immune globulin intravenous, rabies immune globulin (human), respiratory syncytial virus immune globulin intravenous (human), Rh_0(D)

immune globulin (human), $Rh_0(D)$ immune globulin intravenous (human), tetanus immune globulin (human), varicella-zoster immune globulin. The at least one biological response modifiers can be at least one selected from aldesleukin, epoetin alfa, filgrastim, glatiramer acetate for injection, interferon alfacon-1, interferon alfa-2a (recombinant), interferon alfa-2b (recombinant), interferon beta-1a, interferon beta-1b (recombinant), interferon gamma-1b, levamisole hydrochloride, oprelvekin, sargramostim. (See, e.g., pp. 964-1040 of *Nursing 2001 Drug Handbook.*)

The at least one ophthalmic anti-infectives can be selected form bacitracin, chloramphenicol, ciprofloxacin hydrochloride, erythromycin, gentamicin sulfate, ofloxacin 0.3%, polymyxin B sulfate, sulfacetamide sodium 10%, sulfacetamide sodium 15%, sulfacetamide sodium 30%, tobramycin, vidarabine. The at least one ophthalmic anti-inflammatories can be at least one selected from dexamethasone, dexamethasone sodium phosphate, diclofenac sodium 0.1%, fluorometholone, flurbiprofen sodium, ketorolac tromethamine, prednisolone acetate (suspension) prednisolone sodium phosphate (solution). The at least one miotic can be at least one selected from acetylocholine chloride, carbachol (intraocular), carbachol (topical), echothiophate iodide, pilocarpine, pilocarpine hydrochloride, pilocarpine nitrate. The at least one mydriatic can be at least one selected from atropine sulfate, cyclopentolate hydrochloride, epinephrine hydrochloride, epinephryl borate, homatropine hydrobromide, phenylephrine hydrochloride, scopolamine hydrobromide, tropicamide. The at least one ophthalmic vasoconstrictors can be at least one selected from naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride. The at least one miscellaneous ophthalmics can be at least one selected from apraclonidine hydrochloride, betaxolol hydrochloride, brimonidine tartrate, carteolol hydrochloride, dipivefrin hydrochloride, dorzolamide hydrochloride, emedastine difumarate, fluorescein sodium, ketotifen fumarate, latanoprost, levobunolol hydrochloride, metipranolol hydrochloride, sodium chloride (hypertonic), timolol maleate. The at least one otic can be at least one selected from boric acid, carbamide peroxide, chloramphenicol, triethanolamine polypeptide oleate-condensate. The at least one nasal drug can be at least one selected from beclomethasone dipropionate, budesonide, ephedrine sulfate, epinephrine hydrochloride, flunisolide, fluticasone propionate, naphazoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tetrahydrozoline hydrochloride, triamcinolone acetonide, xylometazoline hydrochloride. (See, e.g., pp. 1041-97 of *Nursing 2001 Drug Handbook.*)

The at least one local anti-infectives can be at least one selected from acyclovir, amphotericin B, azelaic acid cream, bacitracin, butoconazole nitrate, clindamycin phosphate, clotrimazole, econazole nitrate, erythromycin, gentamicin sulfate, ketoconazole, mafenide acetate, metronidazole (topical), miconazole nitrate, mupirocin, naftifine hydrochloride, neomycin sulfate, nitrofurazone, nystatin, silver

sulfadiazine, terbinafine hydrochloride, terconazole, tetracycline hydrochloride, tioconazole, tolnaftate. The at least one scabicide or pediculicide can be at least one selected from crotamiton, lindane, permethrin, pyrethrins. The at least one topical corticosteroid can be at least one selected from betamethasone dipropionate, betamethasone valerate, clobetasol propionate, desonide, desoximetasone, dexamethasone, dexamethasone sodium phosphate, diflorasone diacetate, fluocinolone acetonide, fluocinonide, flurandrenolide, fluticasone propionate, halcionide, hydrocortisone, hydrocortisone acetate, hydrocortisone butyrate, hydrocorisone valerate, mometasone furoate, triamcinolone acetonide. (See, e.g., pp. 1098-1136 of *Nursing 2001 Drug Handbook.*)

The at least one vitamin or mineral can be at least one selected from vitamin A, vitamin B complex, cyanocobalamin, folic acid, hydroxocobalamin, leucovorin calcium, niacin, niacinamide, pyridoxine hydrochloride, riboflavin, thiamine hydrochloride, vitamin C, vitamin D, cholecalciferol, ergocalciferol, vitamin D analogue, doxercalciferol, paricalcitol, vitamin E, vitamin K analogue, phytonadione, sodium fluoride, sodium fluoride (topical), trace elements, chromium, copper, iodine, manganese, selenium, zinc. The at least one calorics can be at least one selected from amino acid infusions (crystalline), amino acid infusions in dextrose, amino acid infusions with electrolytes, amino acid infusions with electrolytes in dextrose, amino acid infusions for hepatic failure, amino acid infusions for high metabolic stress, amino acid infusions for renal failure, dextrose, fat emulsions, medium-chain triglycerides. (See, e.g., pp. 1137-63 of *Nursing 2001 Drug Handbook.*)

CNGH0004 antibody or polypeptide compositions of the present invention can further comprise at least one of any suitable and/or effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 protein or antibody to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy, optionally further comprising at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF binding protein I or II (TBP-1 or TBP-II), nerelimonmab, infliximab, enteracept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalzine), a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteriod, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a

thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropieitin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Non-limiting examples of such cytokines include, but are not limted to, any of IL-1 to IL-23. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

Such compositions can also include toxin molecules that are associated, bound, co-formulated or co-administered with at least one antibody or polypeptide of the present invention. The toxin can optionally act to selectively kill the pathologic cell or tissue. The pathologic cell can be a cancer or other cell. Such toxins can be, but are not limited to, purified or recombinant toxin or toxin fragment comprising at least one functional cytotoxic domain of toxin, e.g., selected from at least one of ricin, diphtheria toxin, a venom toxin, or a bacterial toxin. The term toxin also includes both endotoxins and exotoxins produced by any naturally occurring, mutant or recombinant bacteria or viruses which may cause any pathological condition in humans and other mammals, including toxin shock, which can result in death. Such toxins may include, but are not limited to, enterotoxigenic *E. coli* heat-labile enterotoxin (LT), heat-stable enterotoxin (ST), *Shigella* cytotoxin, *Aeromonas* enterotoxins, toxic shock syndrome toxin-1 (TSST-1), Staphylococcal enterotoxin A (SEA), B (SEB), or C (SEC), Streptococcal enterotoxins and the like. Such bacteria include, but are not limited to, strains of a species of enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* (e.g., strains of serotype 0157:H7), Staphylococcus species (e.g., *Staphylococcus aureus, Staphylococcus pyogenes*), *Shigella* species (e.g., *Shigella dysenteriae, Shigella flexneri, Shigella boydii, and Shigella sonnei*), *Salmonella* species (e.g., *Salmonella typhi, Salmonella cholera-suis, Salmonella enteritidis*), *Clostridium* species (e.g., *Clostridium perfringens, Clostridium dificile, Clostridium botulinum*), *Camphlobacter* species (e.g., *Camphlobacter jejuni, Camphlobacter fetus*), *Heliobacter* species, (e.g., *Heliobacter pylori*), *Aeromonas* species (e.g., *Aeromonas sobria, Aeromonas hydrophila, Aeromonas caviae*), *Pleisomonas*

shigelloides, Yersina enterocolitica, Vibrios species (e.g., *Vibrios cholerae, Vibrios parahemolyticus*), *Klebsiella* species, *Pseudomonas aeruginosa*, and *Streptococci*. See, e.g., Stein, ed., INTERNAL MEDICINE, 3rd ed., pp 1-13, Little, Brown and Co., Boston, (1990); Evans et al., eds., Bacterial Infections of Humans: Epidemiology and Control, 2d. Ed., pp 239-254, Plenum Medical Book Co., New York (1991); Mandell et al, Principles and Practice of Infectious Diseases, 3d. Ed., Churchill Livingstone, New York (1990); Berkow et al, eds., *The Merck Manual*, 16th edition, Merck and Co., Rahway, N.J., 1992; Wood et al, FEMS Microbiology Immunology, 76:121-134 (1991); Marrack et al, Science, 248:705-711 (1990), the contents of which references are incorporated entirely herein by reference.

CNGH0004 antibody or polypeptide compounds, compositions or combinations of the present invention can further comprise at least one of any suitable auxiliary, such as, but not limited to, diluent, binder, stabilizer, buffers, salts, lipophilic solvents, preservative, adjuvant or the like. Pharmaceutically acceptable auxiliaries are preferred. Non-limiting examples of, and methods of preparing such sterile solutions are well known in the art, such as, but limited to, Gennaro, Ed., *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Co. (Easton, PA) 1990. Pharmaceutically acceptable carriers can be routinely selected that are suitable for the mode of administration, solubility and/or stability of the CNGH0004 antibody or polypeptide composition as well known in the art or as described herein.

Pharmaceutical excipients and additives useful in the present composition include but are not limited to polypeptides, peptides, amino acids, lipids, and carbohydrates (e.g., sugars, including monosaccharides, di-, tri-, tetra-, and oligosaccharides; derivatized sugars such as alditols, aldonic acids, esterified sugars and the like; and polysaccharides or sugar polymers), which can be present singly or in combination, comprising alone or in combination 1-99.99% by weight or volume. Exemplary but non-limiting polypeptide excipients include serum albumin such as human serum albumin (HSA), recombinant human albumin (rHA), gelatin, casein, and the like. Representative amino acid/antibody components, which can also function in a buffering capacity, include alanine, glycine, arginine, betaine, histidine, glutamic acid, aspartic acid, cysteine, lysine, leucine, isoleucine, valine, methionine, phenylalanine, aspartame, and the like. One preferred amino acid is glycine.

Carbohydrate excipients suitable for use in the invention include, for example, monosaccharides such as fructose, maltose, galactose, glucose, D-mannose, sorbose, and the like; disaccharides, such as lactose, sucrose, trehalose, cellobiose, and the like; polysaccharides, such as raffinose, melezitose, maltodextrins, dextrans, starches, and the like; and alditols, such as mannitol, xylitol, maltitol, lactitol, xylitol sorbitol (glucitol), myoinositol and the like. Preferred carbohydrate

excipients for use in the present invention are mannitol, trehalose, and raffinose.

CNGH0004 antibody or polypeptide compositions can also include a buffer or a pH adjusting agent; typically, the buffer is a salt prepared from an organic acid or base. Representative buffers include organic acid salts such as salts of citric acid, ascorbic acid, gluconic acid, carbonic acid, tartaric acid, succinic acid, acetic acid, or phthalic acid; Tris, tromethamine hydrochloride, or phosphate buffers. Preferred buffers for use in the present compositions are organic acid salts such as citrate.

Additionally, CNGH0004 antibody or polypeptide compositions of the invention can include polymeric excipients/additives such as polyvinylpyrrolidones, ficolls (a polymeric sugar), dextrates (e.g., cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin), polyethylene glycols, flavoring agents, antimicrobial agents, sweeteners, antioxidants, antistatic agents, surfactants (e.g., polysorbates such as "TWEEN 20" and "TWEEN 80"), lipids (*e.g.*, phospholipids, fatty acids), steroids (e.g., cholesterol), and chelating agents (e.g., EDTA).

These and additional known pharmaceutical excipients and/or additives suitable for use in the CNGH0004 antibody or polypeptide compositions according to the invention are known in the art, e.g., as listed in "Remington: The Science & Practice of Pharmacy", 19th ed., Williams & Williams, (1995), and in the "Physician's Desk Reference", 52nd ed., Medical Economics, Montvale, NJ (1998), the disclosures of which are entirely incorporated herein by reference. Preferred carrier or excipient materials are carbohydrates (e.g., saccharides and alditols) and buffers (e.g., citrate) or polymeric agents.

Formulations

As noted above, the invention provides for stable formulations, which is preferably a phosphate buffer with saline or a chosen salt, as well as preserved solutions and formulations containing a preservative as well as multi-use preserved formulations suitable for pharmaceutical or veterinary use, comprising at least one CNGH0004 antibody or polypeptide in a pharmaceutically acceptable formulation. Preserved formulations contain at least one known preservative or optionally selected from the group consisting of at least one phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, phenylmercuric nitrite, phenoxyethanol, formaldehyde, chlorobutanol, magnesium chloride (e.g., hexahydrate), alkylparaben (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof in an aqueous diluent. Any suitable concentration or mixture can be used as known in the art, such as 0.001-5%, or any range or value therein, such as, but not limited to 0.001, 0.003, 0.005, 0.009, 0.01, 0.02, 0.03, 0.05, 0.09, 0.1, 0.2, 0.3, 0.4., 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9,

2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3.0, 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.7, 3.8, 3.9, 4.0, 4.3, 4.5, 4.6, 4.7, 4.8, 4.9, or any range or value therein. Non-limiting examples include, no preservative, 0.1-2% m-cresol (e.g., 0.2, 0.3. 0.4, 0.5, 0.9, 1.0%), 0.1-3% benzyl alcohol (e.g., 0.5, 0.9, 1.1., 1.5, 1.9, 2.0, 2.5%), 0.001-0.5% thimerosal (e.g., 0.005, 0.01), 0.001-2.0% phenol (e.g., 0.05, 0.25, 0.28, 0.5, 0.9, 1.0%), 0.0005-1.0% alkylparaben(s) (e.g., 0.00075, 0.0009, 0.001, 0.002, 0.005, 0.0075, 0.009, 0.01, 0.02, 0.05, 0.075, 0.09, 0.1, 0.2, 0.3, 0.5, 0.75, 0.9, 1.0%), and the like.

As noted above, the invention provides an article of manufacture, comprising packaging material and at least one vial comprising a solution of at least one CNGH0004 antibody or polypeptide with the prescribed buffers and/or preservatives, optionally in an aqueous diluent, wherein said packaging material comprises a label that indicates that such solution can be held over a period of 1, 2, 3, 4, 5, 6, 9, 12, 18, 20, 24, 30, 36, 40, 48, 54, 60, 66, 72 hours or greater. The invention further comprises an article of manufacture, comprising packaging material, a first vial comprising lyophilized at least one CNGH0004 antibody or polypeptide, and a second vial comprising an aqueous diluent of prescribed buffer or preservative, wherein said packaging material comprises a label that instructs a patient to reconstitute the at least one CNGH0004 antibody or polypeptide in the aqueous diluent to form a solution that can be held over a period of twenty-four hours or greater.

The at least one CNGH0004antibody or polypeptide used in accordance with the present invention can be produced by recombinant means, including from mammalian cell or transgenic preparations, or can be purified from other biological sources, as described herein or as known in the art.

The range of at least one CNGH0004 antibody in at least one product of the present invention includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0 ng/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch, pulmonary, transmucosal, or osmotic or micro pump methods.

The range of at least one CNGH0004 antibody in at least one product of the present invention includes amounts yielding upon reconstitution, if in a wet/dry system, concentrations from about 1.0 µg/ml to about 1000 mg/ml, although lower and higher concentrations are operable and are dependent on the intended delivery vehicle, e.g., solution formulations will differ from transdermal patch, pulmonary, transmucosal, or osmotic or micro pump methods.

Preferably, the aqueous diluent optionally further comprises a pharmaceutically acceptable preservative. Preferred preservatives include those selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben (methyl, ethyl, propyl, butyl and

the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal, or mixtures thereof. The concentration of preservative used in the formulation is a concentration sufficient to yield an microbial effect. Such concentrations are dependent on the preservative selected and are readily determined by the skilled artisan.

Other excipients, e.g. isotonicity agents, buffers, antioxidants, preservative enhancers, can be optionally and preferably added to the diluent. An isotonicity agent, such as glycerin, is commonly used at known concentrations. A physiologically tolerated buffer is preferably added to provide improved pH control. The formulations can cover a wide range of pHs, such as from about pH 4 to about pH 10, and preferred ranges from about pH 5 to about pH 9, and a most preferred range of about 6.0 to about 8.0. Preferably the formulations of the present invention have pH between about 6.8 and about 7.8. Preferred buffers include phosphate buffers, most preferably sodium phosphate, particularly phosphate buffered saline (PBS).

Other additives, such as a pharmaceutically acceptable solubilizers like Tween 20 (polyoxyethylene (20) sorbitan monolaurate), Tween 40 (polyoxyethylene (20) sorbitan monopalmitate), Tween 80 (polyoxyethylene (20) sorbitan monooleate), Pluronic F68 (polyoxyethylene polyoxypropylene block copolymers), and PEG (polyethylene glycol) or non-ionic surfactants such as polysorbate 20 or 80 or poloxamer 184 or 188, Pluronic® polyls, other block co-polymers, and chelators such as EDTA and EGTA can optionally be added to the formulations or compositions to reduce aggregation. These additives are particularly useful if a pump or plastic container is used to administer the formulation. The presence of pharmaceutically acceptable surfactant mitigates the propensity for the polypeptide to aggregate.

The formulations of the present invention can be prepared by a process which comprises mixing at least one CNGH0004 antibody or polypeptide and a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, chlorocresol, benzyl alcohol, alkylparaben, (methyl, ethyl, propyl, butyl and the like), benzalkonium chloride, benzethonium chloride, sodium dehydroacetate and thimerosal or mixtures thereof in an aqueous diluent. Mixing the at least one CNGH0004 antibody or polypeptide and preservative in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one CNGH0004 antibody or polypeptide in buffered solution is combined with the desired preservative in a buffered solution in quantities sufficient to provide the polypeptide and preservative at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can

be optimized for the concentration and means of administration used.

The claimed formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one CNGH0004 antibody or polypeptide that is reconstituted with a second vial containing water, a preservative and/or excipients, preferably a phosphate buffer and/or saline and a chosen salt, in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus can provide a more convenient treatment regimen than currently available.

The present claimed articles of manufacture are useful for administration over a period of immediately to twenty-four hours or greater. Accordingly, the presently claimed articles of manufacture offer significant advantages to the patient. Formulations of the invention can optionally be safely stored at temperatures of from about 2 to about 40°C and retain the biologically activity of the polypeptide for extended periods of time, thus, allowing a package label indicating that the solution can be held and/or used over a period of 6, 12, 18, 24, 36, 48, 72, or 96 hours or greater. If preserved diluent is used, such label can include use up to 1-12 months, one-half, one and a half, and/or two years.

The solutions of at least one CNGH0004 antibody or polypeptide in the invention can be prepared by a process that comprises mixing at least one antibody or polypeptide in an aqueous diluent. Mixing is carried out using conventional dissolution and mixing procedures. To prepare a suitable diluent, for example, a measured amount of at least one antibody or polypeptide in water or buffer is combined in quantities sufficient to provide the polypeptide and optionally a preservative or buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The claimed products can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one CNGH0004 antibody or polypeptide that is reconstituted with a second vial containing the aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

The claimed products can be provided indirectly to patients by providing to pharmacies, clinics, or other such institutions and facilities, clear solutions or dual vials comprising a vial of lyophilized at least one CNGH0004 antibody or polypeptide that is reconstituted with a second vial containing the aqueous diluent. The clear solution in this case can be up to one liter or even larger

in size, providing a large reservoir from which smaller portions of the at least one antibody or polypeptide solution can be retrieved one or multiple times for transfer into smaller vials and provided by the pharmacy or clinic to their customers and/or patients.

Recognized devices comprising these single vial systems include those pen-injector devices for delivery of a solution such as BD Pens, BD Autojector®, Humaject®, NovoPen®, B-D®Pen, AutoPen®, and OptiPen®, GenotropinPen®, Genotronorm Pen®, Humatro Pen®, Reco-Pen®, Roferon Pen®, Biojector®, iject®, J-tip Needle-Free Injector®, Intraject®, Medi-Ject®, e.g., as made or developed by Becton Dickensen (Franklin Lakes, NJ, www.bectondickenson.com), Disetronic (Burgdorf, Switzerland, www.disetronic.com; Bioject, Portland, Oregon (www.bioject.com); National Medical Products , Weston Medical (Peterborough, UK, www.weston-medical.com), Medi-Ject Corp (Minneapolis, MN, www.mediject.com). Recognized devices comprising a dual vial system include those pen-injector systems for reconstituting a lyophilized drug in a cartridge for delivery of the reconstituted solution such as the HumatroPen®.

The products presently claimed include packaging material. The packaging material provides, in addition to the information required by the regulatory agencies, the conditions under which the product can be used. The packaging material of the present invention provides instructions to the patient to reconstitute the at least one CNGH0004 antibody or polypeptide in the aqueous diluent to form a solution and to use the solution over a period of 2-24 hours or greater for the two vial, wet/dry, product. For the single vial, solution product, the label indicates that such solution can be used over a period of 2-24 hours or greater. The presently claimed products are useful for human pharmaceutical product use.

The formulations of the present invention can be prepared by a process that comprises mixing at least one CNGH0004 antibody or polypeptide and a selected buffer, preferably a phosphate buffer containing saline or a chosen salt. Mixing the at least one antibody or polypeptide and buffer in an aqueous diluent is carried out using conventional dissolution and mixing procedures. To prepare a suitable formulation, for example, a measured amount of at least one antibody or polypeptide in water or buffer is combined with the desired buffering agent in water in quantities sufficient to provide the polypeptide and buffer at the desired concentrations. Variations of this process would be recognized by one of ordinary skill in the art. For example, the order the components are added, whether additional additives are used, the temperature and pH at which the formulation is prepared, are all factors that can be optimized for the concentration and means of administration used.

The claimed stable or preserved formulations can be provided to patients as clear solutions or as dual vials comprising a vial of lyophilized at least one CNGH0004 antibody or

polypeptide that is reconstituted with a second vial containing a preservative or buffer and excipients in an aqueous diluent. Either a single solution vial or dual vial requiring reconstitution can be reused multiple times and can suffice for a single or multiple cycles of patient treatment and thus provides a more convenient treatment regimen than currently available.

At least one CNGH0004 antibody or polypeptide in either the stable or preserved formulations or solutions described herein, can be administered to a patient in accordance with the present invention via a variety of delivery methods including SC or IM injection; transdermal, pulmonary, transmucosal, implant, osmotic pump, cartridge, micro pump, or other means appreciated by the skilled artisan, as well-known in the art.

Therapeutic Applications

The present invention also provides a method for modulating or treating at least one CNGH0004 related disease, in a cell, tissue, organ, animal, or patient, as known in the art or as described herein, using at least one antibody or polypeptide of the present invention.

The present invention also provides a method for modulating or treating at least one CNGH0004 related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of obesity, an immune related disease, a cardiovascular disease, an infectious disease, a malignant disease or a neurologic disease.

The present invention also provides a method for modulating or treating at least one adult or pediatric immune or inflammation related disease, in a cell, tissue, organ, animal, or patient including, but not limited to, at least one of, or at least one inflammation related to, rheumatoid arthritis, juvenile rheumatoid arthritis, systemic onset juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondilitis, gastric ulcer, seronegative arthropathies, osteoarthritis, inflammatory bowel disease, ulcerative colitis, Crohn's disease, systemic lupus erythematosis, antiphospholipid syndrome, iridocyclitis, uveitis, optic neuritis, idiopathic pulmonary fibrosis, systemic vasculitis, Wegener's granulomatosis, sarcoidosis, orchitis, vasectomy or vasectomy reversal procedures, allergic atopic diseases, asthma, allergic rhinitis, eczema, allergic contact dermatitis, allergic conjunctivitis, hypersensitivity pneumonitis, transplants, organ transplant rejection, graft-versus-host disease, systemic inflammatory response syndrome, sepsis syndrome, gram positive sepsis, gram negative sepsis, culture negative sepsis, fungal sepsis, neutropenic fever, urosepsis, meningococcemia, trauma, hemorrhage, burns, ionizing radiation exposure, acute pancreatitis, adult respiratory distress syndrome, rheumatoid arthritis, alcohol-induced hepatitis, chronic inflammatory pathologies, sarcoidosis, Crohn's pathology, sickle cell anemia, type I or type II diabetes, nephrosis, atopic diseases, hypersensitity

reactions, allergic rhinitis, hay fever, perennial rhinitis, conjunctivitis, endometriosis, asthma, urticaria, systemic anaphalaxis, dermatitis, pernicious anemia, hemolytic disesease, thrombocytopenia, graft rejection of any organ or tissue, kidney translplant rejection, heart transplant rejection, liver transplant rejection, pancreas transplant rejection, lung transplant rejection, bone marrow transplant (BMT) rejection, skin allograft rejection, cartilage transplant rejection, bone graft rejection, small bowel transplant rejection, fetal thymus implant rejection, parathyroid transplant rejection, xenograft rejection of any organ or tissue, allograft rejection, receptor hypersensitivity reactions, chronic obstructive pulmonary disease (COPD), Graves disease, Raynoud's disease, type B insulin-resistant diabetes, asthma, myasthenia gravis, antibody-meditated cytotoxicity, gene therapy inflammation (e.g., adenovirus, AAV, vaccinia, DNA or RNA, Muloney murine leukemia virus (MMLV) and the like), type III hypersensitivity reactions, systemic lupus erythematosus, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome), polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome, antiphospholipid syndrome, pemphigus, scleroderma, mixed connective tissue disease, idiopathic Addison's disease, diabetes mellitus, chronic active hepatitis, primary billiary cirrhosis, vitiligo, vasculitis, post-MI cardiotomy syndrome, type IV hypersensitivity , contact dermatitis, hypersensitivity pneumonitis, allograft rejection, granulomas due to intracellular organisms, drug sensitivity, metabolic, idiopathic, Wilson's disease, hemachromatosis, alpha-1-antitrypsin deficiency, diabetic retinopathy, Hashimoto's thyroiditis, osteoporosis, hypothalamic-pituitary-adrenal axis evaluation, primary biliary cirrhosis, thyroiditis, encephalomyelitis, cachexia, cystic fibrosis, neonatal chronic lung disease, chronic obstructive pulmonary disease (COPD), familial hematophagocytic lymphohistiocytosis, dermatologic conditions, psoriasis, alopecia, nephrotic syndrome, nephritis, glomerular nephritis, acute renal failure, hemodialysis, uremia, toxicity, preeclampsia, okt3 therapy, cd3 therapy, cytokine therapy, chemotherapy, radiation therapy (e.g., including but not limited toasthenia, anemia, cachexia, and the like), chronic salicylate intoxication, and the like. See, e.g., the Merck Manual, 12th-17th Editions, Merck & Company, Rahway, NJ (1972, 1977, 1982, 1987, 1992, 1999), Pharmacotherapy Handbook, Wells et al., eds., Second Edition, Appleton and Lange, Stamford, Conn. (1998, 2000), each entirely incorporated by reference.

The present invention also provides a method for modulating or treating at least one cardiovascular disease in a cell, tissue, organ, animal, or patient, including, but not limited to, at least one of cardiac stun syndrome, myocardial infarction, congestive heart failure, stroke, ischemic stroke, hemorrhage, arteriosclerosis, atherosclerosis, restenosis, diabetic ateriosclerotic disease, hypertension, arterial hypertension, renovascular hypertension, syncope, shock, syphilis of the cardiovascular system,

heart failure, cor pulmonale, primary pulmonary hypertension, cardiac arrhythmias, atrial ectopic beats, atrial flutter, atrial fibrillation (sustained or paroxysmal), post perfusion syndrome, cardiopulmonary bypass inflammation response, chaotic or multifocal atrial tachycardia, regular narrow QRS tachycardia, specific arrythmias, ventricular fibrillation, His bundle arrythmias, atrioventricular block, bundle branch block, myocardial ischemic disorders, coronary artery disease, angina pectoris, myocardial infarction, cardiomyopathy, dilated congestive cardiomyopathy, restrictive cardiomyopathy, valvular heart diseases, endocarditis, pericardial disease, cardiac tumors, aordic and peripheral aneuryisms, aortic dissection, inflammation of the aorta, occulsion of the abdominal aorta and its branches, peripheral vascular disorders, occulsive arterial disorders, peripheral atherlosclerotic disease, thromboangitis obliterans, functional peripheral arterial disorders, Raynaud's phenomenon and disease, acrocyanosis, erythromelalgia, venous diseases, venous thrombosis, varicose veins, arteriovenous fistula, lymphederma, lipedema, unstable angina, reperfusion injury, post pump syndrome, ischemia-reperfusion injury, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

The present invention also provides a method for modulating or treating at least one infectious disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: acute or chronic infection, acute and chronic parasitic or infectious processes, including bacterial, viral and fungal infections, HIV infection, HIV neuropathy, meningitis, hepatitis (A,B or C, or the like), septic arthritis, peritonitis, pneumonia, epiglottitis, e. coli 0157:h7, hemolytic uremic syndrome, thrombolytic thrombocytopenic purpura, malaria, dengue hemorrhagic fever, leishmaniasis, leprosy, toxic shock syndrome, streptococcal myositis, gas gangrene, mycobacterium tuberculosis, mycobacterium avium intracellulare, pneumocystis carinii pneumonia, pelvic inflammatory disease, orchitis, epidydimitis, legionella, lyme disease, influenza a, epstein-barr virus, vital-associated hemaphagocytic syndrome, vital encephalitis, aseptic meningitis, and the like. Such toxins can be, but are not limited to, purified or recombinant toxin or toxin fragment comprising at least one functional cytotoxic domain of toxin, e.g., selected from at least one of diphtheria toxin, a venom toxin, a viral toxin or a bacterial toxin. The term toxin also includes both endotoxins and exotoxins produced by any naturally occurring, mutant or recombinant bacteria or viruses which may cause any pathological condition in humans and other mammals, including toxin shock, which can result in death. Such toxins may include, but are not limited to, enterotoxigenic *E. coli* heat-labile enterotoxin (LT), heat-stable enterotoxin (ST), *Shigella* cytotoxin, *Aeromonas* enterotoxins, toxic shock syndrome toxin-1 (TSST-1), Staphylococcal

enterotoxin A (SEA), B (SEB), or C (SEC), Streptococcal enterotoxins anthrax endotoxin, and the like. Such bacteria include, but are not limited to, gram negative or gram positive bactieria, Bacillus, E. coli, Streptococcus, Staphlococcus, Shigella, Salmonella, Clostridium, Camphbacter, Heliobacter, Aeromonas, Enteroccis, Pseudomonas, and the like, such as but not limited to, strains of a species of enterotoxigenic *E. coli* (ETEC), enterohemorrhagic *E. coli* (e.g., strains of serotype 0157:H7), Staphylococcus species (e.g., *Staphylococcus aureus, Staphylococcus pyogenes*), *Shigella* species (e.g., *Shigella dysenteriae, Shigella flexneri, Shigella boydii, and Shigella sonnei*), *Salmonella* species (e.g., *Salmonella typhi, Salmonella cholera-suis, Salmonella enteritidis*), *Clostridium* species (e.g., *Clostridium perfringens, Clostridium dificile, Clostridium botulinum*), *Camphlobacter* species (e.g., *Camphlobacter jejuni, Camphlobacter fetus*), *Heliobacter* species, (e.g., *Heliobacter pylori*), *Aeromonas* species (e.g., *Aeromonas sobria, Aeromonas hydrophila, Aeromonas caviae*), *Pleisomonas shigelloides, Yersina enterocolitica, Vibrios* species (e.g., *Vibrios cholerae, Vibrios parahemolyticus*), *Klebsiella* species, *Pseudomonas aeruginosa*, and *Streptococci*. See, e.g., Stein, ed., INTERNAL MEDICINE, 3rd ed., pp 1-13, Little, Brown and Co., Boston, (1990); Evans et al., eds., Bacterial Infections of Humans: Epidemiology and Control, 2d. Ed., pp 239-254, Plenum Medical Book Co., New York (1991); Mandell et al, Principles and Practice of Infectious Diseases, 3d. Ed., Churchill Livingstone, New York (1990); Berkow et al, eds., *The Merck Manual*, 16th edition, Merck and Co., Rahway, N.J., 1992; Wood et al, FEMS Microbiology Immunology, 76:121-134 (1991); Marrack et al, Science, 248:705-711 (1990), the contents of which references are incorporated entirely herein by reference. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

The present invention also provides a method for modulating or treating at least one malignant disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: leukemia, acute leukemia, acute lymphoblastic leukemia (ALL), acute lymphocytic leukemia, B-cell, T-cell or FAB ALL, acute myeloid leukemia (AML), acute myelogenous leukemia, chromic myelocytic leukemia (CML), chronic lymphocytic leukemia (CLL), hairy cell leukemia, myelodyplastic syndrome (MDS), a lymphoma, Hodgkin's disease, a malignamt lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, multiple myeloma, Kaposi's sarcoma, colorectal carcinoma, pancreatic carcinoma, nasopharyngeal carcinoma, malignant histiocytosis, paraneoplastic syndrome/hypercalcemia of malignancy, solid tumors, bladder cancer, breast cancer, colorectal cancer, endometiral cancer, head cancer, neck cancer, hereditary nonpolyposis cancer, Hodgkin's lymphoma, liver cancer, lung cancer, non-small cell lung cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma,

testicular cancer, adenocarcinomas, sarcomas, malignant melanoma, hemangioma, metastatic disease, cancer related bone resorption, cancer related bone pain, and the like.

Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy.

The present invention also provides a method for modulating or treating at least one neurologic disease in a cell, tissue, organ, animal or patient, including, but not limited to, at least one of: neurodegenerative diseases, multiple sclerosis, migraine headache, AIDS dementia complex, demyelinating diseases, such as multiple sclerosis and acute transverse myelitis; extrapyramidal and cerebellar disorders' such as lesions of the corticospinal system; disorders of the basal ganglia or cerebellar disorders; hyperkinetic movement disorders such as Huntington's Chorea and senile chorea; drug-induced movement disorders, such as those induced by drugs which block CNS dopamine receptors; hypokinetic movement disorders, such as Parkinson's disease; Progressive supranucleo Palsy; structural lesions of the cerebellum; spinocerebellar degenerations, such as spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, multiple systems degenerations (Mencel, Dejerine-Thomas, Shi-Drager, and Machado-Joseph); systemic disorders (Refsum's disease, abetalipoprotemia, ataxia, telangiectasia, and mitochondrial multi.system disorder); demyelinating core disorders, such as multiple sclerosis, acute transverse myelitis; and disorders of the motor unit' such as neurogenic muscular atrophies (anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy); Alzheimer's disease; Down's Syndrome in middle age; Diffuse Lewy body disease; Senile Dementia of Lewy body type; Wernicke-Korsakoff syndrome; chronic alcoholism; Creutzfeldt-Jakob disease; Subacute sclerosing panencephalitis, Hallerrorden-Spatz disease; and Dementia pugilistica, and the like. Such a method can optionally comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. See, e.g., the Merck Manual, 16th Edition, Merck & Company, Rahway, NJ (1992).

Any method of the present invention can comprise administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. Such a method can optionally further comprise co-administration or combination therapy for treating such diseases, wherein the administering of said at least one CNGH0004 antibody or polypeptide, specified portion or variant thereof, further comprises administering, before concurrently, and/or after,

at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF chemical or protein antagonist, TNF monoclonal or polyclonal antibody or fragment, a soluble TNF receptor (e.g., p55, p70 or p85) or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist, e.g., TNF binding protein I or II (TBP-I or TBP-II), nerelimonmab, infliximab, enteracept, CDP-571, CDP-870, afelimomab, lenercept, and the like), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalzine), a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteriod, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropieitin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist. Suitable dosages are well known in the art. See, e.g., Wells et al., eds., Pharmacotherapy Handbook, 2nd Edition, Appleton and Lange, Stamford, CT (2000); PDR Pharmacopoeia, Tarascon Pocket Pharmacopoeia 2000, Deluxe Edition, Tarascon Publishing, Loma Linda, CA (2000), each of which references are entirely incorporated herein by reference.

TNF antagonists suitable for compositions, combination therapy, co-administration, devices and/or methods of the present invention (further comprising at least one anti body, specified portion and variant thereof, of the present invention), include, but are not limited to, TNF antibodies, antigen-binding fragments thereof, and receptor molecules which bind specifically to TNF; compounds which prevent and/or inhibit TNF synthesis, TNF release or its action on target cells, such as thalidomide, tenidap, phosphodiesterase inhibitors (e.g, pentoxifylline and rolipram), A2b adenosine receptor agonists and A2b adenosine receptor enhancers; compounds which prevent and/or inhibit TNF receptor signalling, such as mitogen activated polypeptide (MAP) kinase inhibitors; compounds which block and/or inhibit membrane TNF cleavage, such as metallopolypeptidease inhibitors; compounds which

block and/or inhibit TNF activity, such as angiotensin converting enzyme (ACE) inhibitors (e.g., captopril); and compounds which block and/or inhibit TNF production and/or synthesis, such as MAP kinase inhibitors.

As used herein, a "tumor necrosis factor antibody," "TNF antibody," "TNFα antibody," or fragment and the like decreases, blocks, inhibits, abrogates or interferes with TNFα activity *in vitro, in situ* and/or preferably in *vivo*. For example, a suitable TNF human antibody of the present invention can bind TNFα and includes TNF antibodies, antigen-binding fragments thereof, and specified mutants or domains thereof that bind specifically to TNFα. A suitable TNF anttibody or fragment can also decrease block, abrogate, interfere, prevent and/or inhibit TNF RNA, DNA or polypeptide synthesis, TNF release, TNF receptor signaling, membrane TNF cleavage, TNF activity, TNF production and/or synthesis.

Chimeric antibody cA2 consists of the antigen binding variable region of the high-affinity neutralizing mouse human TNFα IgG1 antibody, designated A2, and the constant regions of a human IgG1, kappa immunoglobulin. The human IgG1 Fc region improves allogeneic antibody effector function, increases the circulating serum half-life and decreases the immunogenicity of the antibody. The avidity and epitope specificity of the chimeric antibody cA2 is derived from the variable region of the murine antibody A2. In a particular embodiment, a preferred source for nucleic acids encoding the variable region of the murine antibody A2 is the A2 hybridoma cell line.

Chimeric A2 (cA2) neutralizes the cytotoxic effect of both natural and recombinant human TNFα in a dose dependent manner. From binding assays of chimeric antibody cA2 and recombinant human TNFα, the affinity constant of chimeric antibody cA2 was calculated to be $1.04 \times 10^{10} M^{-1}$. Preferred methods for determining monoclonal antibody specificity and affinity by competitive inhibition can be found in Harlow, *et al., antibodies: A Laboratory Manual,* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1988; Colligan *et al.*, eds., *Current Protocols in Immunology,* Greene Publishing Assoc. and Wiley Interscience, New York, (1992-2000); Kozbor *et al., Immunol. Today, 4*:72-79 (1983); Ausubel *et al.*, eds. *Current Protocols in Molecular Biology,* Wiley Interscience, New York (1987-2000); and Muller, *Meth. Enzymol., 92*:589-601 (1983), which references are entirely incorporated herein by reference.

In a particular embodiment, murine monoclonal antibody A2 is produced by a cell line designated c134A. Chimeric antibody cA2 is produced by a cell line designated c168A.

Additional examples of monoclonal TNF antibodies that can be used in the present invention are described in the art (see, e.g., U.S. Patent No. 5,231,024; Möller, A. *et al., Cytokine 2*(3):162-169 (1990); U.S. Application No. 07/943,852 (filed September 11, 1992); Rathjen *et al.*, International

Publication No. WO 91/02078 (published February 21, 1991); Rubin *et al.*, EPO Patent Publication No. 0 218 868 (published April 22, 1987); Yone *et al.*, EPO Patent Publication No. 0 288 088 (October 26, 1988); Liang, *et al.*, *Biochem. Biophys. Res. Comm. 137*:847-854 (1986); Meager, *et al.*, *Hybridoma 6*:305-311 (1987); Fendly *et al.*, *Hybridoma 6*:359-369 (1987); Bringman, *et al.*, *Hybridoma 6*:489-507 (1987); and Hirai, *et al.*, *J. Immunol. Meth. 96*:57-62 (1987), which references are entirely incorporated herein by reference).

TNF Receptor Molecules

Preferred TNF receptor molecules useful in the present invention are those that bind TNFα with high affinity (see, e.g., Feldmann *et al.*, International Publication No. WO 92/07076 (published April 30, 1992); Schall *et al.*, *Cell 61*:361-370 (1990); and Loetscher *et al.*, *Cell 61*:351-359 (1990), which references are entirely incorporated herein by reference) and optionally possess low immunogenicity. In particular, the 55 kDa (p55 TNF-R) and the 75 kDa (p75 TNF-R) TNF cell surface receptors are useful in the present invention. Truncated forms of these receptors, comprising the extracellular domains (ECD) of the receptors or functional portions thereof (see, e.g., Corcoran *et al.*, *Eur. J. Biochem. 223*:831-840 (1994)), are also useful in the present invention. Truncated forms of the TNF receptors, comprising the ECD, have been detected in urine and serum as 30 kDa and 40 kDa TNFα inhibitory binding polypeptides (Engelmann, H. *et al.*, *J. Biol. Chem. 265*:1531-1536 (1990)). TNF receptor multimeric molecules and TNF immunoreceptor fusion molecules, and derivatives and fragments or portions thereof, are additional examples of TNF receptor molecules which are useful in the methods and compositions of the present invention. The TNF receptor molecules which can be used in the invention are characterized by their ability to treat patients for extended periods with good to excellent alleviation of symptoms and low toxicity. Low immunogenicity and/or high affinity, as well as other undefined properties, can contribute to the therapeutic results achieved.

TNF receptor multimeric molecules useful in the present invention comprise all or a functional portion of the ECD of two or more TNF receptors linked via one or more polypeptide linkers or other nonpeptide linkers, such as polyethylene glycol (PEG). The multimeric molecules can further comprise a signal peptide of a secreted polypeptide to direct expression of the multimeric molecule. These multimeric molecules and methods for their production have been described in U.S. Application No. 08/437,533 (filed May 9, 1995), the content of which is entirely incorporated herein by reference.

TNF immunoreceptor fusion molecules useful in the methods and compositions of the present invention comprise at least one portion of one or more immunoglobulin molecules and all or a functional portion of one or more TNF receptors. These immunoreceptor fusion molecules can be assembled as monomers, or hetero- or homo-multimers. The immunoreceptor fusion molecules can

also be monovalent or multivalent. An example of such a TNF immunoreceptor fusion molecule is TNF receptor/IgG fusion polypeptide. TNF immunoreceptor fusion molecules and methods for their production have been described in the art (Lesslauer *et al.*, *Eur. J. Immunol. 21*:2883-2886 (1991); Ashkenazi *et al.*, *Proc. Natl. Acad. Sci. USA 88*:10535-10539 (1991); Peppel *et al.*, *J. Exp. Med. 174*:1483-1489 (1991); Kolls *et al.*, *Proc. Natl. Acad. Sci. USA 91*:215-219 (1994); Butler *et al.*, *Cytokine 6*(6):616-623 (1994); Baker *et al.*, *Eur. J. Immunol. 24*:2040-2048 (1994); Beutler *et al.*, U.S. Patent No. 5,447,851; and U.S. Application No. 08/442,133 (filed May 16, 1995), each of which references are entirely incorporated herein by reference). Methods for producing immunoreceptor fusion molecules can also be found in Capon *et al.*, U.S. Patent No. 5,116,964; Capon *et al.*, U.S. Patent No. 5,225,538; and Capon *et al.*, *Nature 337*:525-531 (1989), which references are entirely incorporated herein by reference.

A functional equivalent, derivative, fragment or region of TNF receptor molecule refers to the portion of the TNF receptor molecule, or the portion of the TNF receptor molecule sequence which encodes TNF receptor molecule, that is of sufficient size and sequences to functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNF? with high affinity and possess low immunogenicity). A functional equivalent of TNF receptor molecule also includes modified TNF receptor molecules that functionally resemble TNF receptor molecules that can be used in the present invention (e.g., bind TNF? with high affinity and possess low immunogenicity). For example, a functional equivalent of TNF receptor molecule can contain a "SILENT" codon or one or more amino acid substitutions, deletions or additions (e.g., substitution of one acidic amino acid for another acidic amino acid; or substitution of one codon encoding the same or different hydrophobic amino acid for another codon encoding a hydrophobic amino acid). See Ausubel *et al.*, *Current Protocols in Molecular Biology*, Greene Publishing Assoc. and Wiley-Interscience, New York (1987-2000).

Cytokines include any known cytokine. See, e.g., CopewithCytokines.com. Cytokine antagonists include, but are not limited to, any antibody, fragment or mimetic, any soluble receptor, fragment or mimetic, any small molecule antagonist, or any combination thereof.

Therapeutic Treatments. Any method of the present invention can comprise a method for treating a CNGH0004 mediated disorder or disease, comprising administering an effective amount of a composition or pharmaceutical composition comprising at least one CNGH0004 antibody or polypeptide to a cell, tissue, organ, animal or patient in need of such modulation, treatment or therapy. Such a method can optionally further comprise co-administration or combination therapy for treating such disorders or diseases, wherein the administering of said at least one CNGH0004 antibody or

polypeptide, further comprises administering, before concurrently, and/or after, at least one selected from at least one at least one selected from at least one TNF antagonist (e.g., but not limited to a TNF antibody or fragment, a soluble TNF receptor or fragment, fusion polypeptides thereof, or a small molecule TNF antagonist), an antirheumatic (e.g., methotrexate, auranofin, aurothioglucose, azathioprine, etanercept, gold sodium thiomalate, hydroxychloroquine sulfate, leflunomide, sulfasalzine), a muscle relaxant, a narcotic, a non-steroid inflammatory drug (NSAID), an analgesic, an anesthetic, a sedative, a local anethetic, a neuromuscular blocker, an antimicrobial (e.g., aminoglycoside, an antifungal, an antiparasitic, an antiviral, a carbapenem, cephalosporin, a flurorquinolone, a macrolide, a penicillin, a sulfonamide, a tetracycline, another antimicrobial), an antipsoriatic, a corticosteriod, an anabolic steroid, a diabetes related agent, a mineral, a nutritional, a thyroid agent, a vitamin, a calcium related hormone, an antidiarrheal, an antitussive, an antiemetic, an antiulcer, a laxative, an anticoagulant, an erythropieitin (e.g., epoetin alpha), a filgrastim (e.g., G-CSF, Neupogen), a sargramostim (GM-CSF, Leukine), an immunization, an immunoglobulin, an immunosuppressive (e.g., basiliximab, cyclosporine, daclizumab), a growth hormone, a hormone replacement drug, an estrogen receptor modulator, a mydriatic, a cycloplegic, an alkylating agent, an antimetabolite, a mitotic inhibitor, a radiopharmaceutical, an antidepressant, antimanic agent, an antipsychotic, an anxiolytic, a hypnotic, a sympathomimetic, a stimulant, donepezil, tacrine, an asthma medication, a beta agonist, an inhaled steroid, a leukotriene inhibitor, a methylxanthine, a cromolyn, an epinephrine or analog, dornase alpha (Pulmozyme), a cytokine or a cytokine antagonist.

Polypeptide Dosing

Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one CNGH0004 polypeptide composition that total, on average, a range from at least about 0.001 ng to 500 milligrams of at least one CNGH0004 polypeptide per kilogram of patient per dose, and preferably from at least about 0.1 ng to 100 milligrams antibody /kilogram of patient per single or multiple administration, depending upon the specific activity of contained in the composition. Alternatively, the effective serum concentration can comprise 0.0001ng –0.05 mg/ml serum concentration per single or multiple adminstration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, *i.e.*, repeated individual administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired daily dose or effect is achieved.

Preferred doses of at least one polypeptide can optionally include 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 and/or 100-500 micrograms or milligrams/kg/administration, or any range, value or fraction thereof, or to achieve a serum concentration of 0.1, 0.5, 0.9, 1.0, 1.1, 1.2, 1.5, 1.9, 2.0, 2.5, 2.9, 3.0, 3.5, 3.9, 4.0, 4.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 20, 12.5, 12.9, 13.0, 13.5, 13.9, 14.0, 14.5, 4.9, 5.0, 5.5., 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 12, 12.5, 12.9, 13.0, 13.5, 13.9, 14, 14.5, 15, 15.5, 15.9, 16, 16.5, 16.9, 17, 17.5, 17.9, 18, 18.5, 18.9, 19, 19.5, 19.9, 20, 20.5, 20.9, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, and/or 5000 ng or μg/ml serum concentration per single or multiple administration, or any range, value or fraction thereof.

Alternatively, the dosage administered can vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a dosage of active ingredient can be about 0.1 μg to 100 milligrams per kilogram of body weight. Ordinarily 0.0001 to 50, and preferably 0.001 to 10 milligrams per kilogram per administration or in sustained release form is effective to obtain desired results.

As a non-limiting example, treatment of humans or animals can be provided as a one-time or periodic dosage of at least one antibody of the present invention 0.1 to 100 μg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 2000 or 3000 μg/kg, per day, or 0.1 to 100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively or additionally, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, or alternatively or additionally, at least one of 1, 2, 3, 4, 5, 6,, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 years, or any combination thereof, using single, infusion or repeated doses.

Dosage forms (composition) suitable for internal administration generally contain from about 0.00001 milligram to about 500 milligrams of active ingredient per unit or container. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-99.999% by weight based on the total weight of the composition.

Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one CNGH0004 antibody composition that total, on average, a range from at least about 0.00001 to 500 milligrams of at least one CNGH0004antibody per kilogram of patient per dose, and preferably from at least about 0.0001 to 100 milligrams antibody /kilogram of patient per single or multiple administration, depending upon the specific activity of contained in the composition. Alternatively, the effective serum concentration can comprise 0.0001-500 μg/ml serum concentration per single or multiple adminstration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, *i.e.*, repeated individual administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired daily dose or effect is achieved.

Antibody Dosing

Typically, treatment of pathologic conditions is effected by administering an effective amount or dosage of at least one CNGH0004 antibody composition that total, on average, a range from at least about 0.001 ng to 500 milligrams of at least one CNGH0004antibody per kilogram of patient per dose, and preferably from at least about 0.1 ng to 100 milligrams antibody /kilogram of patient per single or multiple administration, depending upon the specific activity of contained in the composition. Alternatively, the effective serum concentration can comprise 0.0001ng –0.05 mg/ml serum concentration per single or multiple adminstration. Suitable dosages are known to medical practitioners and will, of course, depend upon the particular disease state, specific activity of the composition being administered, and the particular patient undergoing treatment. In some instances, to achieve the desired therapeutic amount, it can be necessary to provide for repeated administration, *i.e.*, repeated individual administrations of a particular monitored or metered dose, where the individual administrations are repeated until the desired daily dose or effect is achieved.

Preferred doses of at least one antibody can optionally include 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87,

88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99 and/or 100-500 mg/kg/administration, or any range, value or fraction thereof, or to achieve a serum concentration of 0.1, 0.5, 0.9, 1.0, 1.1, 1.2, 1.5, 1.9, 2.0, 2.5, 2.9, 3.0, 3.5, 3.9, 4.0, 4.5, 4.9, 5.0, 5.5, 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 20, 12.5, 12.9, 13.0, 13.5, 13.9, 14.0, 14.5, 4.9, 5.0, 5.5., 5.9, 6.0, 6.5, 6.9, 7.0, 7.5, 7.9, 8.0, 8.5, 8.9, 9.0, 9.5, 9.9, 10, 10.5, 10.9, 11, 11.5, 11.9, 12, 12.5, 12.9, 13.0, 13.5, 13.9, 14, 14.5, 15, 15.5, 15.9, 16, 16.5, 16.9, 17, 17.5, 17.9, 18, 18.5, 18.9, 19, 19.5, 19.9, 20, 20.5, 20.9, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 96, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 2500, 3000, 3500, 4000, 4500, and/or 5000 μg/ml serum concentration per single or multiple administration, or any range, value or fraction thereof.

Alternatively, the dosage administered can vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent, and its mode and route of administration; age, health, and weight of the recipient; nature and extent of symptoms, kind of concurrent treatment, frequency of treatment, and the effect desired. Usually a dosage of active ingredient can be about 0.1 to 100 milligrams per kilogram of body weight. Ordinarily 0.1 to 50, and preferably 0.1 to 10 milligrams per kilogram per administration or in sustained release form is effective to obtain desired results.

As a non-limiting example, treatment of humans or animals can be provided as a one-time or periodic dosage of at least one antibody of the present invention 0.1 to 100 mg/kg, such as 0.5, 0.9, 1.0, 1.1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 mg/kg, per day, on at least one of day 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40, or alternatively or additionally, at least one of week 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, or 52, or alternatively or additionally, at least one of 1, 2, 3, 4, 5, 6,, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 years, or any combination thereof, using single, infusion or repeated doses.

Dosage forms (composition) suitable for internal administration generally contain from about 0.1 milligram to about 500 milligrams of active ingredient per unit or container. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5-99.999% by weight based on the total weight of the composition.

Administration

For parenteral administration, the antibody or polypeptide can be formulated as a solution, suspension, emulsion or lyophilized powder in association, or separately provided, with a

pharmaceutically acceptable parenteral vehicle. Examples of such vehicles are water, saline, Ringer's solution, dextrose solution, and 1-10% human serum albumin. Liposomes and nonaqueous vehicles such as fixed oils can also be used. The vehicle or lyophilized powder can contain additives that maintain isotonicity (e.g., sodium chloride, mannitol) and chemical stability (e.g., buffers and preservatives). The formulation is sterilized by known or suitable techniques.

Suitable pharmaceutical carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, A. Osol, a standard reference text in this field.

Alternative Administration

Many known and developed modes of can be used according to the present invention for administering pharmaceutically effective amounts of at least one CNGH0004 antibody according to the present invention. While pulmonary administration is used in the following description, other modes of administration can be used according to the present invention with suitable results.

CNGH0004 antibodies of the present invention can be delivered in a carrier, as a solution, emulsion, colloid, or suspension, or as a dry powder, using any of a variety of devices and methods suitable for administration by inhalation or other modes described here within or known in the art.

Parenteral Formulations and Administration

Formulations for parenteral administration can contain as common excipients sterile water or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, hydrogenated naphthalenes and the like. Aqueous or oily suspensions for injection can be prepared by using an appropriate emulsifier or humidifier and a suspending agent, according to known methods. Agents for injection can be a non-toxic, non-orally administrable diluting agent such as aquous solution or a sterile injectable solution or suspension in a solvent. As the usable vehicle or solvent, water, Ringer's solution, isotonic saline, etc. are allowed; as an ordinary solvent, or suspending solvent, sterile involatile oil can be used. For these purposes, any kind of involatile oil and fatty acid can be used, including natural or synthetic or semisynthetic fatty oils or fatty acids; natural or synthetic or semisynthtetic mono- or di- or tri-glycerides. Parental administration is known in the art and includes, but is not limited to, conventional means of injections, a gas pressured needle-less injection device as described in U.S. Pat. No. 5,851,198, and a laser perforator device as described in U.S. Pat. No. 5,839,446 entirely incorporated herein by reference.

Alternative Delivery

The invention further relates to the administration of at least one CNGH0004 antibody by parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic,

intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal means. At least one CNGH0004 antibody composition can be prepared for use for parenteral (subcutaneous, intramuscular or intravenous) or any other administration particularly in the form of liquid solutions or suspensions; for use in vaginal or rectal administration particularly in semisolid forms such as, but not limited to, creams and suppositories; for buccal, or sublingual administration such as, but not limited to, in the form of tablets or capsules; or intranasally such as, but not limited to, the form of powders, nasal drops or aerosols or certain agents; or transdermally such as not limited to a gel, ointment, lotion, suspension or patch delivery system with chemical enhancers such as dimethyl sulfoxide to either modify the skin structure or to increase the drug concentration in the transdermal patch (Junginger, et al. In "Drug Permeation Enhancement"; Hsieh, D. S., Eds., pp. 59-90 (Marcel Dekker, Inc. New York 1994, entirely incorporated herein by reference), or with oxidizing agents that enable the application of formulations containing polypeptides and peptides onto the skin (WO 98/53847), or applications of electric fields to create transient transport pathways such as electroporation, or to increase the mobility of charged drugs through the skin such as iontophoresis, or application of ultrasound such as sonophoresis (U.S. Pat. Nos. 4,309,989 and 4,767,402) (the above publications and patents being entirely incorporated herein by reference).

Pulmonary/Nasal Administration

For pulmonary administration, preferably at least one CNGH0004 antibody composition is delivered in a particle size effective for reaching the lower airways of the lung or sinuses. According to the invention, at least one CNGH0004 antibody can be delivered by any of a variety of inhalation or nasal devices known in the art for administration of a therapeutic agent by inhalation. These devices capable of depositing aerosolized formulations in the sinus cavity or alveoli of a patient include metered dose inhalers, nebulizers, dry powder generators, sprayers, and the like. Other devices suitable for directing the pulmonary or nasal administration of antibodies are also known in the art. All such devices can use of formulations suitable for the administration for the dispensing of antibody in an aerosol. Such aerosols can be comprised of either solutions (both aqueous and non aqueous) or solid particles. Metered dose inhalers like the Ventolin® metered dose inhaler, typically use a propellent gas and require actuation during inspiration (See, e.g., WO 94/16970, WO 98/35888). Dry powder inhalers like Turbuhaler™ (Astra), Rotahaler® (Glaxo), Diskus® (Glaxo), Spiros™ inhaler (Dura), devices marketed by Inhale Therapeutics, and the Spinhaler® powder inhaler (Fisons), use breath-actuation of a mixed powder (US 4668218 Astra, EP 237507 Astra, WO 97/25086 Glaxo, WO

94/08552 Dura, US 5458135 Inhale, WO 94/06498 Fisons, entirely incorporated herein by reference). Nebulizers like AERx™ Aradigm, the Ultravent® nebulizer (Mallinckrodt), and the Acorn II® nebulizer (Marquest Medical Products) (US 5404871 Aradigm, WO 97/22376), the above references entirely incorporated herein by reference, produce aerosols from solutions, while metered dose inhalers, dry powder inhalers, etc. generate small particle aerosols. These specific examples of commercially available inhalation devices are intended to be a representative of specific devices suitable for the practice of this invention, and are not intended as limiting the scope of the invention. Preferably, a composition comprising at least one CNGH0004 antibody is delivered by a dry powder inhaler or a sprayer. There are a several desirable features of an inhalation device for administering at least one antibody of the present invention. For example, delivery by the inhalation device is advantageously reliable, reproducible, and accurate. The inhalation device can optionally deliver small dry particles, e.g. less than about 10 μm, preferably about 1-5 μm, for good respirability.

Administration of CNGH0004 antibody Compositions as a Spray

A spray including CNGH0004 antibody composition can be produced by forcing a suspension or solution of at least one CNGH0004 antibody through a nozzle under pressure. The nozzle size and configuration, the applied pressure, and the liquid feed rate can be chosen to achieve the desired output and particle size. An electrospray can be produced, for example, by an electric field in connection with a capillary or nozzle feed. Advantageously, particles of at least one CNGH0004 antibody composition delivered by a sprayer have a particle size less than about 10 μm, preferably in the range of about 1 μm to about 5 μm, and most preferably about 2 μm to about 3 μm.

Formulations of at least one CNGH0004 polypeptide or antibody composition suitable for use with a sprayer typically include antibody or polypeptide compositions in an aqueous solution at a concentration of about 0.0000001 mg to about 1000 mg of at least one CNGH0004 antibody or polypeptide composition per ml of solution or mg/gm, or any range or value therein, e.g., but not lmited to, .1, .2., .3, .4, .5, .6, .7, .8, .9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 40, 45, 50, 60, 70, 80, 90 or 100 ng or μg or mg/ml or ng or μg or mg/gm. The formulation can include agents such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and, preferably, zinc. The formulation can also include an excipient or agent for stabilization of the antibody composition, such as a buffer, a reducing agent, a bulk polypeptide, or a carbohydrate. Bulk polypeptides useful in formulating antibody compositions include albumin, protamine, or the like. Typical carbohydrates useful in formulating antibody compositions include sucrose, mannitol, lactose, trehalose, glucose, or the like. The antibody composition formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the antibody or

polypeptide composition caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid esters and alcohols, and polyoxyethylene sorbitol fatty acid esters. Amounts will generally range between 0.001 and 14% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan monooleate, polysorbate 80, polysorbate 20, or the like. Additional agents known in the art for formulation of a polypeptide such as CNGH0004 antibodies, or specified portions or variants, can also be included in the formulation.

Administration of CNGH0004 antibody compositions by a Nebulizer

Antibody composition can be administered by a nebulizer, such as jet nebulizer or an ultrasonic nebulizer. Typically, in a jet nebulizer, a compressed air source is used to create a high-velocity air jet through an orifice. As the gas expands beyond the nozzle, a low-pressure region is created, which draws a solution of antibody composition through a capillary tube connected to a liquid reservoir. The liquid stream from the capillary tube is sheared into unstable filaments and droplets as it exits the tube, creating the aerosol. A range of configurations, flow rates, and baffle types can be employed to achieve the desired performance characteristics from a given jet nebulizer. In an ultrasonic nebulizer, high-frequency electrical energy is used to create vibrational, mechanical energy, typically employing a piezoelectric transducer. This energy is transmitted to the formulation of antibody composition either directly or through a coupling fluid, creating an aerosol including the antibody composition. Advantageously, particles of antibody composition delivered by a nebulizer have a particle size less than about 10 μm, preferably in the range of about 1 μm to about 5 μm, and most preferably about 2 μm to about 3 μm.

Formulations of at least one CNGH0004 antibody suitable for use with a nebulizer, either jet or ultrasonic, typically include a concentration of about 0.1 mg to about 100 mg of at least one CNGH0004 antibody polypeptide per ml of solution. The formulation can include agents such as an excipient, a buffer, an isotonicity agent, a preservative, a surfactant, and, preferably, zinc. The formulation can also include an excipient or agent for stabilization of the at least one CNGH0004 antibody composition, such as a buffer, a reducing agent, a bulk polypeptide, or a carbohydrate. Bulk polypeptides useful in formulating at least one CNGH0004 antibody compositions include albumin, protamine, or the like. Typical carbohydrates useful in formulating at least one CNGH0004 antibody include sucrose, mannitol, lactose, trehalose, glucose, or the like. The at least one CNGH0004 antibody formulation can also include a surfactant, which can reduce or prevent surface-induced aggregation of the at least one CNGH0004 antibody caused by atomization of the solution in forming an aerosol. Various conventional surfactants can be employed, such as polyoxyethylene fatty acid

esters and alcohols, and polyoxyethylene sorbital fatty acid esters. Amounts will generally range between 0.001 and 4% by weight of the formulation. Especially preferred surfactants for purposes of this invention are polyoxyethylene sorbitan mono-oleate, polysorbate 80, polysorbate 20, or the like. Additional agents known in the art for formulation of a polypeptide such as antibody polypeptide can also be included in the formulation.

Administration of CNGH0004 antibody compositions By A Metered Dose Inhaler

In a metered dose inhaler (MDI), a propellant, at least one CNGH0004 antibody, and any excipients or other additives are contained in a canister as a mixture including a liquefied compressed gas. Actuation of the metering valve releases the mixture as an aerosol, preferably containing particles in the size range of less than about 10 μm, preferably about 1 μm to about 5 μm, and most preferably about 2 μm to about 3 μm. The desired aerosol particle size can be obtained by employing a formulation of antibody composition produced by various methods known to those of skill in the art, including jet-milling, spray drying, critical point condensation, or the like. Preferred metered dose inhalers include those manufactured by 3M or Glaxo and employing a hydrofluorocarbon propellant.

Formulations of at least one CNGH0004 antibody for use with a metered-dose inhaler device will generally include a finely divided powder containing at least one CNGH0004 antibody as a suspension in a non-aqueous medium, for example, suspended in a propellant with the aid of a surfactant. The propellant can be any conventional material employed for this purpose, such as chlorofluorocarbon, a hydrochlorofluorocarbon, a hydrofluorocarbon, or a hydrocarbon, including trichlorofluoromethane, dichlorodifluoromethane, dichlorotetrafluoroethanol and 1,1,1,2-tetrafluoroethane, HFA-134a (hydrofluroalkane-134a), HFA-227 (hydrofluroalkane-227), or the like. Preferably the propellant is a hydrofluorocarbon. The surfactant can be chosen to stabilize the at least one CNGH0004 antibody as a suspension in the propellant, to protect the active agent against chemical degradation, and the like. Suitable surfactants include sorbitan trioleate, soya lecithin, oleic acid, or the like. In some cases solution aerosols are preferred using solvents such as ethanol. Additional agents known in the art for formulation of a polypeptide such as polypeptide can also be included in the formulation.

One of ordinary skill in the art will recognize that the methods of the current invention can be achieved by pulmonary administration of at least one CNGH0004 antibody compositions via devices not described herein.

Oral Formulations and Administration

Formulations for oral rely on the co-administration of adjuvants (e.g., resorcinols and nonionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase

artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF) and trasylol) to inhibit enzymatic degradation. The active constituent compound of the solid-type dosage form for oral administration can be mixed with at least one additive, including sucrose, lactose, cellulose, mannitol, trehalose, raffinose, maltitol, dextran, starches, agar, arginates, chitins, chitosans, pectins, gum tragacanth, gum arabic, gelatin, collagen, casein, albumin, synthetic or semisynthetic polymer, and glyceride. These dosage forms can also contain other type(s) of additives, e.g., inactive diluting agent, lubricant such as magnesium stearate, paraben, preserving agent such as sorbic acid, ascorbic acid, .alpha.-tocopherol, antioxidant such as cysteine, disintegrator, binder, thickener, buffering agent, sweetening agent, flavoring agent, perfuming agent, etc.

Tablets and pills can be further processed into enteric-coated preparations. The liquid preparations for oral administration include emulsion, syrup, elixir, suspension and solution preparations allowable for medical use. These preparations can contain inactive diluting agents ordinarily used in said field, e.g., water. Liposomes have also been described as drug delivery systems for insulin and heparin (U.S. Pat. No. 4,239,754). More recently, microspheres of artificial polymers of mixed amino acids (polypeptideoids) have been used to deliver pharmaceuticals (U.S. Pat. No. 4,925,673). Furthermore, carrier compounds described in U.S. Pat. No. 5,879,681 and U.S. Pat. No. 5,5,871,753 are used to deliver biologically active agents orally are known in the art.

Mucosal Formulations and Administration

For absorption through mucosal surfaces, compositions and methods of administering at least one CNGH0004 antibody include an emulsion comprising a plurality of submicron particles, a mucoadhesive macromolecule, a bioactive peptide, and an aqueous continuous phase, which promotes absorption through mucosal surfaces by achieving mucoadhesion of the emulsion particles (U.S. Pat. Nos. 5,514,670). Mucous surfaces suitable for application of the emulsions of the present invention can include corneal, conjunctival, buccal, sublingual, nasal, vaginal, pulmonary, stomachic, intestinal, and rectal routes of administration. Formulations for vaginal or rectal administration, e.g. suppositories, can contain as excipients, for example, polyalkyleneglycols, vaseline, cocoa butter, and the like. Formulations for intranasal administration can be solid and contain as excipients, for example, lactose or can be aqueous or oily solutions of nasal drops. For buccal administration excipients include sugars, calcium stearate, magnesium stearate, pregelinatined starch, and the like (U.S. Pat. Nos. 5,849,695).

Transdermal Formulations and Administration

For transdermal administration, the at least one CNGH0004 antibody is encapsulated in a

delivery device such as a liposome or polymeric nanoparticles, microparticle, microcapsule, or microspheres (referred to collectively as microparticles unless otherwise stated). A number of suitable devices are known, including microparticles made of synthetic polymers such as polyhydroxy acids such as polylactic acid, polyglycolic acid and copolymers thereof, polyorthoesters, polyanhydrides, and polyphosphazenes, and natural polymers such as collagen, polyamino acids, albumin and other polypeptides, alginate and other polysaccharides, and combinations thereof (U.S. Pat. Nos. 5,814,599).

Prolonged Administration and Formulations

It can be sometimes desirable to deliver the compounds of the present invention to the subject over prolonged periods of time, for example, for periods of one week to one year from a single administration. Various slow release, depot or implant dosage forms can be utilized. For example, a dosage form can contain a pharmaceutically acceptable non-toxic salt of the compounds that has a low degree of solubility in body fluids, for example, (a) an acid addition salt with a polybasic acid such as phosphoric acid, sulfuric acid, citric acid, tartaric acid, tannic acid, pamoic acid, alginic acid, polyglutamic acid, naphthalene mono- or di-sulfonic acids, polygalacturonic acid, and the like; (b) a salt with a polyvalent metal cation such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel, cadmium and the like, or with an organic cation formed from e.g., N,N'-dibenzyl-ethylenediamine or ethylenediamine; or (c) combinations of (a) and (b) e.g. a zinc tannate salt. Additionally, the compounds of the present invention or, preferably, a relatively insoluble salt such as those just described, can be formulated in a gel, for example, an aluminum monostearate gel with, e.g. sesame oil, suitable for injection. Particularly preferred salts are zinc salts, zinc tannate salts, pamoate salts, and the like. Another type of slow release depot formulation for injection would contain the compound or salt dispersed for encapsulated in a slow degrading, non-toxic, non-antigenic polymer such as a polylactic acid/polyglycolic acid polymer for example as described in U.S. Pat. No. 3,773,919. The compounds or, preferably, relatively insoluble salts such as those described above can also be formulated in cholesterol matrix silastic pellets, particularly for use in animals. Additional slow release, depot or implant formulations, e.g. gas or liquid liposomes are known in the literature (U.S. Pat. Nos. 5,770,222 and "Sustained and Controlled Release Drug Delivery Systems", J. R. Robinson ed., Marcel Dekker, Inc., N.Y., 1978).

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Example 1: Cloning and Expression of CNGH0004 polypeptide or antibody in Mammalian Cells

A typical mammalian expression vector contains at least one promoter element, which mediates the initiation of transcription of mRNA, the polypeptide or antibody coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription can be achieved with the early and late promoters from SV40, the long terminal repeats (LTRS) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter). Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pIRES1neo, pRetro-Off, pRetro-On, PLXSN, or pLNCX (Clonetech Labs, Palo Alto, CA), pcDNA3.1 (+/-), pcDNA/Zeo (+/-) or pcDNA3.1/Hygro (+/-) (Invitrogen), PSVL and PMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146) and pBC12MI (ATCC 67109). Mammalian host cells that could be used include human Hela 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV 1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the gene can be expressed in stable cell lines that contain the gene integrated into a chromosome. The co-transfection with a selectable marker such as dhfr, gpt, neomycin, or hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded polypeptide or antibody, e.g., as a desired portion of at least one of SEQ ID NO:1. The DHFR (dihydrofolate reductase) marker is useful to develop cell lines that carry several hundred or even several thousand copies of the gene of interest. Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy, et al., Biochem. J. 227:277-279 (1991); Bebbington, et al., Bio/Technology 10:169-175 (1992)). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are used for the production of antibodies or polypeptides of the present invention.

The expression vectors pC1 and pC4 contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen, et al., Molec. Cell. Biol. 5:438-447 (1985)) plus a fragment of the CMV-enhancer (Boshart, et al., Cell 41:521-530 (1985)). Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors contain in addition the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene.

Cloning and Expression in CHO Cells

The vector pC4 is used for the expression of CNGH0004 antibody or polypeptide, e.g., using a coding sequence for at least one of SEQ ID NO:1, such as but not limited to SEQ ID NO:2. Plasmid pC4 is a derivative of the plasmid pSV2-dhfr (ATCC Accession No. 37146). The plasmid contains the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary- or other cells lacking dihydrofolate activity that are transfected with these plasmids can be selected by growing the cells in a selective medium (e.g., alpha minus MEM, Life Technologies, Gaithersburg, MD) supplemented with the chemotherapeutic agent methotrexate. The amplification of the DHFR genes in cells resistant to methotrexate (MTX) has been well documented (see, e.g., F. W. Alt, et al., J. Biol. Chem. 253:1357-1370 (1978); J. L. Hamlin and C. Ma, Biochem. et Biophys. Acta 1097:107-143 (1990); and M. J. Page and M. A. Sydenham, Biotechnology 9:64-68 (1991)). Cells grown in increasing concentrations of MTX develop resistance to the drug by overproducing the target enzyme, DHFR, as a result of amplification of the DHFR gene. If a second gene is linked to the DHFR gene, it is usually co-amplified and over-expressed. It is known in the art that this approach can be used to develop cell lines carrying more than 1,000 copies of the amplified gene(s). Subsequently, when the methotrexate is withdrawn, cell lines are obtained that contain the amplified gene integrated into one or more chromosome(s) of the host cell.

Plasmid pC4 contains coding DNA for expressing the gene of interest under control of the strong promoter of the long terminal repeat (LTR) of the Rous Sarcoma Virus (Cullen, et al., Molec. Cell. Biol. 5:438-447 (1985)) plus a fragment isolated from the enhancer of the immediate early gene of human cytomegalovirus (CMV) (Boshart, et al., Cell 41:521-530 (1985)). Downstream of the promoter are BamHI, XbaI, and Asp718 restriction enzyme cleavage sites that allow integration of the genes. Behind these cloning sites the plasmid contains the 3' intron and polyadenylation site of the rat preproinsulin gene. Other high efficiency promoters can also be used for the expression, e.g., the human b-actin promoter, the SV40 early or late promoters or the long terminal repeats from other retroviruses, e.g., HIV and HTLVI. Clontech's Tet-Off and Tet-On gene expression systems and similar systems can be used to express the CNGH0004 polypeptide in a regulated way in mammalian cells (M. Gossen, and H. Bujard, Proc. Natl. Acad. Sci. USA 89: 5547-5551 (1992)). For the polyadenylation of the mRNA other signals, e.g., from the human growth hormone or globin genes can be used as well. Stable cell lines carrying a gene of interest integrated into the chromosomes can also be selected upon co-transfection with a selectable marker such as gpt, G418 or hygromycin. It can be advantageous to use more than one selectable marker in the beginning, e.g., G418 plus methotrexate.

The plasmid pC4 is digested with restriction enzymes and then dephosphorylated using calf

intestinal phosphatase by procedures known in the art. The vector is then isolated from a 1% agarose gel.

The DNA sequence encoding the desired CNGH0004 antibody or polypeptide is used, e.g., DNA or RNA coding for at least one of SEQ ID NO:1, such as but not limited to SEQ ID NO:2 corresponding to at least one portion of at least one CNGH0004 antibody polypeptide of the present invention, according to known method steps.

The isolated encoding DNA and the dephosphorylated vector are then ligated with T4 DNA ligase. E. coli HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC4 using, for instance, restriction enzyme analysis.

Chinese hamster ovary (CHO) cells lacking an active DHFR gene are used for transfection. 5 μg of the expression plasmid pC4 is cotransfected with 0.5 μg of the plasmid pSV2-neo using lipofectin. The plasmid pSV2neo contains a dominant selectable marker, the neo gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 μg /ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of methotrexate plus 1 μg /ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 mM, 2 mM, 5 mM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained that grow at a concentration of 100 - 200 mM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reverse phase HPLC analysis.

Example 2: Discovery of CNGH0004 nucleic acid and amino acid sequences and fragments and domains thereof

Skin biopsy samples were collected from patients with moderate to severe psoriasis. Seven samples were obtained at baseline (week 0) from lesional sites. Five were obtained from lesional site at 2 weeks post-infliximab treatment. Total RNA were extracted from each biopsy sample and were hybridized to two different types of cDNA arrays. RNA preparation, labeling, and hybridization were performed as reported previously (9). Raw intensity data from the cDNA arrays were first normalized within each sample. Linear normalization and then nonlinear normalization was performed within each sample. Outlier intensity data points (greater than 1.4 fold away from the median of replicate

measurements) were identified and removed from the data sets. The average intensity was generated by calculating the arithmetic mean of nonoutlier intensity values. Spline normalization of the average intensity was then performed across all samples in the data sets. Sample comparison was made between week 0 and week 2.

Data mining was performed using OmniViz software (Maynard, MA). Data comparisons were expressed as ratios in OmniViz and the $\log_2$ of ratios were used to cluster expression data. Clustering was performed first using the Kmeans method. All genes were filtered by a single fold change greater than or equal to 2 for either increase or decrease in expression. Genes that past the filters were then clustered using a hierarchical method and correlation metric.

Description of CNGH0004 gene

CNGH0004 is located on Chromosome 9q31.3, from nucleotide 1065860007 to 106800277 on the minus strand based on the human reference sequence (UCSC version hg15, which is based on NCBI Build 33 and was produced by the International Human Genome Sequencing Consortium). The human genome sequence covers about 99 percent of the gene-containing regions in the genome, and has been sequenced to an accuracy of 99.99 percent. CNGH0004 neighbors MUSK gene at 5' end and TXN gene at 3' end. The gene is 214270 base pairs long, spreading over three BACS, AL592463, AL354982, and AL158158 from 5' to 3'.

Known mRNAs mapped to this region include Homo sapiens likely ortholog of mouse polydom (NM_024500), Homo sapiens cDNA FLJ14964 fis(AK027870), Homo sapiens mRNA full length insert cDNA clone EUROIMAGE 248114 (AL079279), Homo sapiens serologically defined breast cancer antigen NY-BR-38 mRNA (AF308289), and Homo sapiens cDNA FLJ13529 fis (AK023591).

CNGH0004 transcript is 11,996 bp long. The transcript includes 5' UTR of 1000 bp, 48 exons, and 3' UTR of 280 bp. The ployA signal sequence is not identified.

Polymorphism analysis against public SNP database (http://www.ncbi.nlm.nih.gov/SNP/) as well as NM_024500 revealed 12 SNPs within CNGH0004 coding region (CDS). Eight of the 12 changes result in non-synonymous changes at amino acid level (Table 1).

Conceptual translation of CNGH0004 results in a polypeptide of 3571 amino acid residues. It shares 81.7% residues with mouse Polydom (10) across the entire length and seems to be an ortholog of the mouse protein.

Both proteins share significant overall domain structures: an N-terminal signal peptide followed by a Von Willebrand factor (VWA) domain, 3 CCP (Sushi) domains, 2 Hyalin domains, 1 more CCP domain, 6 EGF-like domains, a Pentaxin domain, 2 more CCP domains, one EGF-like

domain, 28 more CCP domains, and 3 more EGF-like domains at the very C-terminus. There is another unclassified cystein-rich domain (pfam-B 232) that repeated 4 times at the N-terminal portion of the protein (Table 2).

Sequence analysis shows that CNGH0004 and mouse Polydom represent a new sub-family within the EGF superfamily of protein. The members of this sub-family include Q9VM55 of *Drosophia melanogaster,* and Q20535 of *C. elegans*. The common signature of this family is a combination of CCP, EGF-like and Hyalin domain, often repeated many times. Based on the distribution pattern of these domains in other proteins, CNGH0004 protein can be classified as a secreted extracellular matrix protein probably involvs in tissue remodeling.

VWA domains in extracellular eukaryotic proteins mediate adhesion via metal ion-dependent adhesion sites (MIDAS). It has been implicateed in the immune and haemostatic systems, cell adhesion or matrix assembly (11).

CCP domain, also known as Sushi repeat or short complement-like repeat (SCR), is approximately 60 amino acid residues long and has been identified in most components and regulatory proteins of the complement cascade. Prototype members of this protein family are molecules that regulate the complement system (12, 13). CCP repeats have also been identified in the selectin family of adhesion molecules. CCP modules contain proteins of the complement system (14).

Hyalin Repeat, also known as HYR domain, is named after the protein hyalin that is composed exclusively of this repeat. This domain probably corresponds to a new superfamily in the immunoglobulin fold. This domain may be involved in cell adhesion (15).

EGF-like (including EGF_CA) domain is found in the sequence of epidermal growth factor (EGF) and in a large number of membrane-bound and extracellular proteins with various biological functions such as blood coagulation, control of cell fate, cell adhesion, activation of complement and fibrinolysis (16, 17). Many of these proteins require calcium for their biological function. A calcium-binding site has been found to be located at the N-terminus of the EGF-like domains. Calcium-binding may be crucial for numerous protein-protein interactions.

Pentaxins (or pentraxins) are a family of proteins that show, under electron microscope, a discoid arrangement of five noncovalently bound subunits. Proteins of the pentaxin family are involved in acute immunological responses. PTX domain mediates binding of a variety of ligands which is Calcium-dependent (18).

Example 3: Expression of CNGH0004 in normal and diseased human tisuuses

We queried microarray expression database at Johnson & Johnson Pharmaceutical R&D at La

Jolla, as well as public expression database such as SAGE (http://www.ncbi.nlm.nih.gov/SAGE/). CNGH0004 gene is expressed at a high level in normal placenta and fetal tissues. It's at a lower, but detectable level in adult tissues including breast, ear, heart, pancreas, nose, and brain tissues.

We validated the above findings with real-time quatitative PCR using ABI Prism 7900 Sequence Detection System (Applied Biosystems, Foster City, CA). Human tissue master plate was prepared according to Pinhasov et al (19). Total RNA from 83 representative human tissues was purchased from Strategene (La Jolla, CA).

Two primer-probe sets were ordered from from Applied Biosystem as their Assays-on-Demand™ Gene Expression Products (Foster City, CA): Hs00225829_m1, which covers sequence GGTGTGTGGAGCGCCACTGTTCCAC that correspond to 2475 –2499 of CNGH0004; and Hs00295944_m1, which covers sequence ATGCAAAGAGACCAGGTGTGAAACT that corespnd to 10879 –10903 of CNGH0004. As shown in Table 3, both primer-probes sets yield similar results that are in agreement with in silico findings.

Expression of CNGH0004 in most human tissues is very low (table 3). Moderate expression can be detected in adrenal, colon, lung, ovary, pericardium, skin, spleen, stomach, testis, and thymus. The highest expression by far is in placenta, which is at least over 20-fold increase compared to those tissues with moderate expression. CNGH0004 is virtually undetectable in the 10 cell lines we tested.

In certain cancer tissues, however, CNGH0004 expression is significantly elevated. These include glioblastoma, melanoma, colon epithelia, prostate carcinoma, ovary serous adenocarcinoma, pancreas neoplasia, and stomach adeno-carcinoma.

CNGH0004 is also detected at above normal levels in asthmatic airway smooth muscle cells.

Expression level of CNGH0004 is lower in psoriastic lesional areas as compared to non-lesional areas. REMICADE treatment restores its level back to normal.

Example 4: CNGH0004 involvement in cell migration and invasion of metastasis tumors

The establishment of metastasis requires that tumor cells acquire new adhesion and migration properties to emigrate from primary sites and colonize distant organs. CNGH0004 is a cell membrane protein often overexpressed on tumor cells and, being both a cell-cell and cell-extracellular matrix adhesion protein, is well positioned to contribute to this process. Indeed, a fragment of CNGH0004 was identified as serologically defined breast cancer antigen NY-BR-38 mRNA. Furthermore, the interaction of CNGH0004 with other cellular proteins involved in motogenesis and proteolysis is a determinant factor in cell migration and invasion.

The role of CNGH0004 in angiogenesis can also be investigated using *in vitro* cell migration

and invasion assays. Human microvascular endothelial cells (HMVEC) transfected with CNGH0004 gene, or its antisense, or siRNA constructs, are seeded in the top wells of the transwell system, in cell medium containing 1% FBS. In the bottom wells, culturing medium with 10% FBS serve as a chemotactic source to induce cell migration or invasion. The top and bottom wells are separated by a membrane with pores of 8 μm in diameter. The membrane is either uncoated or coated with various extracellular matrix proteins, i.e., collagen, fibronectin, vitronectin, or Matrigel, for determining cell migration or invasion. It is expected that modulation of CNGH0004 changes the properties of endothelial cell migration and invasion stimulation. The specificity of CNGH0004 in endothelial cell migration and invasion are investigated using CNGH0004 antibody of the present invention. Such antibodies block at least one biological activity of CNGH0004.

Advantage/Utilities

CNGH0004 gene is a human ortholog of the mouse Polydom gene. After conceptual translation, the two proteins share extensive homology (81.7%) that is also reflected on their protein domain patterns. The extremely high evolutional conservation implied that the function of CNGH0004 and Polydom is essential to human and mouse, respectively. It is also evident from its ubiquitous expression pattern in embryonic tissues in human and mouse.

Based on N-terminal signal peptide, CNGH0004 protein is predicted to be an extracellular matrix protein. All CNGH0004 protein domains are characterized as extracellular domains.

With 10 EGF domains, which tend to be glycosylated, CNGH0004 is likely to be post-translationally modified (PTM), such as glycosylation. With its high molecular weight and the possible PTM, CNGH0004 is likely distributed in the vicinity of cells that express it. As a target, it is amendable for localized treatment such as subcutaneous injection. Since it is accessible for antagonists and agonists thereto including monoclonal antibodies, vaccines, and adjuvants. CNGH0004 can well be suited for an antibody target.

In addition to normal placenta and fetal tissue development, protein domains that constitute CNGH0004 are probably also involved in tissue remodeling of airway smooth muscle as well as psoriatic epithelium. Based on its domain structure, CNGH0004 may function through mediating adhesion via metal ion-dependent adhesion sites (MIDAS), or via modulating complement control related to immunological responses. As such, CNGH0004 is a potential therapeutic target for treatment of autoimmune or chronic inflammatory diseases including, but not limited to psoriasis or asthma, and different types of cancers.

Table 1. Non-synonymous SNPs within CNGH0004

Nucleotide position	Nucleotide change	Amino acid position	Amino acid change
2286	C->T	429	Ser->Leu
2519	G->A	507	Val->Ile
3526	C->G	842	Cys ->Trp
3939	A->G	980	Glu ->Gly
4188	A->G	1063	Tyr->Cyc
5246	A->C	1416	Lys->Gln
5325	A->T	1442	Asp->Val
6429	C->A	A1810E	Ala->Glu

Table 2. Protein domains and locations on CNGH0004.

Domain Name	Pfam ID	Start residue	End residue
Signal Peptide		1	41
VWA		83	259
Pfam-B 232		305	360
Sushi/CCP	PF00084	378	433
Sushi/CCP	PF00084	438	493
Sushi/CCP	PF00084	498	559
HYR	PF02494	561	642
HYR	PF02494	643	722
CCP	PF00084	727	787
Pfam-B_232		999	1036
Pfam-B_232		1041	1106
Pfam-B_232		1108	1160
EGF-like	PF00008	1196	1229
EGF-like	PF00008	1231	1267
EGF-like	PF00008	1269	1305
EGF-like	PF00008	1307	1343
EGF-like	PF00008	1345	1381

EGF-like	PF00008	1383	1419
Pentaxin		1431	1623
Sushi/CCP	PF00084	1631	1685
Sushi/CCP	PF00084	1690	1743
EGF-like	PF00008	1748	1784
Sushi/CCP	PF00084	1789	1842
Sushi/CCP	PF00084	1847	1900
Sushi/CCP	PF00084	1905	1958
Sushi/CCP	PF00084	1963	2016
Sushi/CCP	PF00084	2021	2078
Sushi/CCP	PF00084	2083	2141
Sushi/CCP	PF00084	2146	2199
Sushi/CCP	PF00084	2204	2259
Sushi/CCP	PF00084	2264	2318
Sushi/CCP	PF00084	2323	2376
Sushi/CCP	PF00084	2381	2435
Sushi/CCP	PF00084	2440	2493
Sushi/CCP	PF00084	2498	2551
Sushi/CCP	PF00084	2556	2608
Sushi/CCP	PF00084	2660	2712
Sushi/CCP	PF00084	2717	2770
Sushi/CCP	PF00084	2775	2828
Sushi/CCP	PF00084	2833	2886
Sushi/CCP	PF00084	2891	2944
Sushi/CCP	PF00084	2949	3002
Sushi/CCP	PF00084	3007	3059
Sushi/CCP	PF00084	3064	3117
Sushi/CCP	PF00084	3122	3176
Sushi/CCP	PF00084	3181	3236
Sushi/CCP	PF00084	3241	3294
Sushi/CCP	PF00084	3299	3352
Sushi/CCP	PF00084	3357	3411
Sushi/CCP	PF00084	3416	3468

EGF-like	PF00008	3468	3499
EGF-like	PF00008	3504	3531
EGF-like	PF00008	3536	3563

Table 3. Relative expression of CNGH0004 in 82 human tissues *

Human RNA	Hs00295944	Hs00225829
Adrenal, Female, Adult	10.03	8.38
Aorta, Female, Fetal	1.00	1.00
Bladder, Male, Adult	6.77	5.27
Bladder, Diseased, Male, Adult	1.42	0.51
Bladder, Female, Fetal	11.07	9.16
Bladder, Male, Fetal	9.54	7.75
Brain, Female, Fetal	1.85	1.39
Brain, Male, Adult	2.38	1.79
Brain, Male, Fetal	0.87	0.95
Brain, Occipital Cortex, Male, Adult	2.78	2.43
Brain, Parietal Cortex, Male, Adult	2.08	2.05
Breast, Female, Adult	6.02	4.89
Caval Vein, Male, Adult	7.86	6.16
Cervix, Female, Adult	6.30	5.13
Colon, Female, Adult (Top)	57.59	54.30
Colon, Ascending, Female, Adult	7.68	5.97
Colon, Decending, Female, Adult	6.26	5.10
Colon, Normal, Male, Adult (Matched Set)	5.46	4.44
Colon, Diseased, Male, Adult (Matched Set)	5.48	4.62
Colon, Female, Fetal	9.62	7.86
Colon, Male, Adult	4.57	3.46
Colon, Male, Adult (Normal)	7.15	5.95
Colon, Male, Adult (Diseased)	4.98	4.13
Colon, Male, Fetal	8.78	6.81
Heart, Female, Adult	1.65	1.61
Heart, Female, Fetal	5.91	4.83
Heart, Left Atrium, Male, Adult	2.53	2.26
Heart, Male, Adult	3.59	3.26
Ileum, Diseased, Male, Adult	3.07	2.17
Ileum, Diseased, Male, Adult (Matched Set)	3.45	2.52
Ileum, Diseased, Male, Adult (Matched Set)	2.88	1.86
Kidney, Female, Fetal	4.42	3.28
Kidney, Diseased, Female, Adult (Matched Set)	8.34	6.60
Kidney, Diseased, Female, Adult (Matched Set)	3.91	3.60
Kidney, Female, Adult	7.48	5.65
Kidney, Male, Adult	1.28	0.98
Kidney, Male, Fetal	7.10	5.89
Larynx, Diseased, Male, Adult (Matched Set)	4.74	3.67
Larynx, Diseased, Male, Adult (Matched Set)	2.66	0.91
Larynx, Male, Adult	5.52	4.38
Larynx, Male, Adult	2.84	0.92
Larynx, Male, Adult (Normal)	9.50	7.67
Liver, Female, Adult	0.91	0.61
Liver, Female, Fetal	1.44	1.19
Liver, Male, Adult	3.75	3.03

Liver, Male, Fetal	1.69	1.36
Lung, Female, Adult	17.53	14.73
Lung, Female, Fetal	3.14	3.04
Lung, Male, Adult	11.47	9.77
Lung, Male, Fetal	8.69	7.67
Lymph Node, Male, Adult	2.33	1.79
Ovary, Female, Adult	23.13	17.83
Pancreas, Male, Adult	3.58	3.34
Parotid, Female, Adult	0.86	0.70
Penis, Male, Adult	8.64	6.83
Pericardium, Male, Adult	20.82	17.52
Placenta, Adult, Female	301.40	312.48
Prostate, Male, Adult	0.70	0.49
Rectum, Male, Adult	4.45	3.24
Skeletal Muscle, Female, Fetal	9.23	7.83
Skeletal Muscle, Male, Adult	6.32	5.32
Skeletal Muscle, Male, Fetal	9.57	8.85
Skin, Female, Adult	4.58	3.77
Skin, Female, Fetal	16.90	14.71
Skin, Male, Adult	28.13	23.60
Spleen, Female, Adult	5.82	4.61
Spleen, Female/Male pooled, Fetal	20.46	18.03
Spleen, Male, Adult	8.03	6.06
Stomach, Diseased, Female, Adult (Matched Set)	4.42	3.58
Stomach, Diseased, Female, Adult (Matched Set)	7.31	5.46
Stomach, Female, Adult	1.76	1.59
Stomach, Female, Fetal	13.89	10.74
Stomach, Male, Adult	3.12	2.12
Stomach, Male, Fetal	10.54	8.70
Testes, Male, Adult	14.52	12.14
Thymus, Male and Female, Fetal	1.21	0.89
Thymus, Male, Adult	15.42	12.14
Thyroid, Female, Adult	5.45	4.17
Tongue, Male/Female, Adult	7.27	5.91
Trachea, Female, Adult	5.90	4.60
Uterus, Female, Adult	7.94	5.72
Vulva, Diseased, Female, Adult	1.51	0.71

* Relative expression is calculated using a formula according to manufacturer's instruction (User Bulletin #2: ABI PRISM 7700 Sequence Detection System, Applied Biosystems, Foster City, CA). Evaluation of the copy number of mRNA of our gene of interest, CNGH0004, in specific tissues examined as shown in the table was compared with that of a calibrator tissue, in this case, Female Fetal Aorta.

It will be clear that the invention can be practiced otherwise than as particularly described in the foregoing description and examples.

Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

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WHAT IS CLAIMED IS:

1. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide comprising or complementary to the all of the contiguous nucleic acids 1001-11713 of SEQ ID NO:1.

2. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide comprising or complementary to at least 45 contiguous nucleotides 1001-11713 of SEQ ID NO:1.

3. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide encoding the amino acid sequence of SEQ ID NO:2, or a polynucleotide complementary thereto.

4. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide having at least 95-99% identity to a nucleotide sequence comprising or complementary to all of the contiguous nucleotides 1001-11713 of SEQ ID NO:1.

5. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide having at least 95-99% identity to a nucleotide sequence comprising or complementary to at least 45 of the contiguous nucleotides 1001-11713 of SEQ ID NO:1.

6. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide that hybridizes under stringent conditions to all of the contiguous nucleotides of SEQ ID NO:1 or a polynucleotide complementary thereto.

7. At least one CNGH0004 nucleic acid, comprising at least one polynucleotide that hybridizes under stringent conditions to at least 45 contiguous nucleotides of SEQ ID NO:1 or a polynucleotide complementary thereto.

8. At least one CNGH0004 polypeptide, comprising all of the contiguous amino acids of SEQ ID NO:2.

9. At least one CNGH0004 polypeptide, comprising at least 15 contiguous amino acids of SEQ ID NO:2.

10. At least one CNGH0004 polypeptide, comprising at least one domain of SEQ ID NO:2.

11. At least one CNGH0004 polypeptide, comprising at least one polypeptide having at least 90-99% identity to an amino acid sequence comprising all of the contiguous amino acids of SEQ ID NO:2.

12. At least one CNGH0004 polypeptide, comprising at least one polypeptide having at least 90-99% identity to an amino acid sequence comprising at least 15 of the

contiguous amino acids of SEQ ID NO:2.

13. At least one CNGH0004 polypeptide, comprising at least one polypeptide encoded by at least one polynucleotide that hybridizes under stringent conditions to all of the contiguous nucleotides SEQ ID NO:1 or a polynucleotide complementary thereto.

14. At least one CNGH0004 polypeptide, comprising at least one polypeptide encoded by at least one polynucleotide that hybridizes under stringent conditions to at least 45 of the contiguous nucleotides SEQ ID NO:1 or a polynucleotide complementary thereto.

15. At least one CNGH0004 polypeptide, comprising at least one of 1-82, 83-259, 259-377, 378-433, 434-438, 438-493, 498-559, 1631-1685, 1690-1743, 1789-1842, 2021-2078, 2083-2141, 2146-2199, 2204-2259, 2264-2318, 2323-2376, 2381-2435, 2440-2493, 2498-2551, 2556-2608, 2660-2712, 2717-2770, 2775-2828, 2833-2886, 2891-2944, 2949-3002, 3007-3059, 3064-3117, 3122-3176, 3181-3236, 3241-3294, 3299-3352, 3357-3411, 3416-3468, 1231-1267, 1269-1305, 1307-1343, 1345-1381, 1383-1419, 1748-1784, 3468-3499, 3504-3531, 3536-3563, 1431-1623, 643-722, 561-642, 1196-1229, 727-787, 1847-1900, 1963-2016, 1905-1958, 999-1036, 1041-1106, 1108-1160, 1-41, or 305-360 of SEQ ID NO:1.

16. A CNGH0004 nucleic acid or CNGH0004 polypeptide according to any of claims 1-15, wherein said polypeptide has at least one activity of at least one CNGH0004 polypeptide.

17. A CNGH0004 antibody, comprising a monoclonal or polyclonal antibody, fusion protein, or fragment thereof, that specifically binds at least one CNGH0004 polypeptide according to any of claims 1-15.

18. A CNGH0004 nucleic acid encoding at least one CNGH0004 polypeptide or CNGH0004 antibody according to any of claim 1-17.

19. A CNGH0004 vector comprising at least one isolated nucleic acid according to any of claims 1-7.

20. A CNGH0004 host cell comprising an isolated nucleic acid according to claim 18.

21. A CNGH0004 host cell according to claim 20, wherein said host cell is at least one selected from COS-1, COS-7, HEK293, BHK21, CHO, BSC-1, Hep G2, 653, SP2/0, 293, NSO, DG44 CHO, CHO K1, HeLa, myeloma, or lymphoma cells, or any derivative, immortalized or transformed cell thereof.

22. A method for producing at least one CNGH0004 polypeptide or CNGH0004 antibody, comprising translating a nucleic acid according to claim 18 under conditions in

vitro, in vivo or in situ, such that the CNGH0004 polypeptide is expressed in detectable or recoverable amounts.

23. A composition comprising at least one CNGH0004 nucleic acid, CNGH0004 polypeptide, or CNGH0004 antibody according to any of claims 1-17.

24. A composition according to claim 23, wherein said composition further comprises at least one pharmaceutically acceptable carrier or diluent.

25. A composition according to claim 23, further comprising at least one composition comprising an therapeutically effective amount of at least one compound, composition or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplactic, an immunomodulation drug, an opthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

26. A composition according to claim 23, in a form of at least one selected from a liquid, gas, or dry, solution, mixture, suspension, emulsion or colloid, a lyophilized preparation, a powder.

27. A method for diagnosing or treating a CNGH0004 related condition in a cell, tissue, organ or animal, comprising

(a) contacting or administering a composition comprising an effective amount of at least one CNGH0004 nucleic acid, polypeptide or antibody according to any of claims 1-17, with, or to, said cell, tissue, organ or animal.

28. A method according to claim 27, wherein said effective amount is 0.001-50 mg of CNGH0004 antibody; 0.000001-500 mg of said CNGH0004 polypeptide; or 0.0001-100μg of said CNGH0004 nucleic acid per kilogram of said cells, tissue, organ or animal.

29. A method according to claim 27, wherein said contacting or said administrating is by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

30. A method according to claim 27, further comprising administering, prior, concurrently or after said (a) contacting or administering, at least one composition comprising an effective amount of at least one compound or polypeptide selected from at least one of a detectable label or reporter, a TNF antagonist, an anti-infective drug, a cardiovascular (CV) system drug, a central nervous system (CNS) drug, an autonomic nervous system (ANS) drug, a respiratory tract drug, a gastrointestinal (GI) tract drug, a hormonal drug, a drug for fluid or electrolyte balance, a hematologic drug, an antineoplactic, an immunomodulation drug, an opthalmic, otic or nasal drug, a topical drug, a nutritional drug, a cytokine, or a cytokine antagonist.

31. A device, comprising at least one isolated CNGH0004 polypeptide, antibody or nucleic acid according to any of claims 1-17, wherein said device is suitable for contacting or administerting said at least one of said CNGH0004 polypeptide, antibody or nucleic acid, by at least one mode selected from parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal.

32. An article of manufacture for human pharmaceutical or diagnostic use, comprising packaging material and a container comprising at least one isolated CNGH0004 polypeptide, antibody or nucleic acid according to any of claims 1-17.

33. The article of manufacture of claim 32, wherein said container is a component of a parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar, intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, intralesional, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal delivery device or system.

34. A method for producing at least one isolated CNGH0004 polypeptide, antibody or nucleic acid according to any of claims 1-17, comprising providing at least one host cell, transgenic animal, transgenic plant, plant cell capable of expressing in detectable or recoverable amounts said polypeptide, antibody or nucleic acid.

35. At least one CNGH0004 polypeptide, antibody or nucleic acid, produced by a method according to claim 34.

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aac tca ggg gct gaa ttg gtc att acc aga agt cat aca caa gga gac     3079
Asn Ser Gly Ala Glu Leu Val Ile Thr Arg Ser His Thr Gln Gly Asp
        680                 685                 690
ctt ttc cct caa ggg gag act ata gta cag tat aca gcc act gac ccc     3127
Leu Phe Pro Gln Gly Glu Thr Ile Val Gln Tyr Thr Ala Thr Asp Pro
    695                 700                 705
tca ggc aat aac agg aca tgt gat atc cat att gtc ata aaa ggt tct     3175
Ser Gly Asn Asn Arg Thr Cys Asp Ile His Ile Val Ile Lys Gly Ser
710                 715                 720                 725
ccc tgt gaa att cca ttc aca cct gta aat ggg gat ttt ata tgc act     3223
Pro Cys Glu Ile Pro Phe Thr Pro Val Asn Gly Asp Phe Ile Cys Thr
                730                 735                 740
cca gat aat act gga gtc aac tgt aca tta act tgc ttg gag ggc tat     3271
Pro Asp Asn Thr Gly Val Asn Cys Thr Leu Thr Cys Leu Glu Gly Tyr
            745                 750                 755
gat ttc aca gaa ggg tct act gac aag tat tat tgt gct tat gaa gat     3319
Asp Phe Thr Glu Gly Ser Thr Asp Lys Tyr Tyr Cys Ala Tyr Glu Asp
        760                 765                 770
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ggc gtc tgg aaa cca aca tat acc act gaa tgg cca gac tgt gcc aaa     3367
Gly Val Trp Lys Pro Thr Tyr Thr Thr Glu Trp Pro Asp Cys Ala Lys
    775                 780                 785
aaa cgt ttt gca aac cac ggg ttc aag tcc ttt gag atg ttc tac aaa     3415
Lys Arg Phe Ala Asn His Gly Phe Lys Ser Phe Glu Met Phe Tyr Lys
790                 795                 800                 805
gca gct cgt tgt gat gac aca gat ctg atg aag aag ttt tct gaa gca     3463
Ala Ala Arg Cys Asp Asp Thr Asp Leu Met Lys Lys Phe Ser Glu Ala
                810                 815                 820
ttt gag acg acc ctg gga aaa atg gtc cca tca ttt tgt agt gat gca     3511
Phe Glu Thr Thr Leu Gly Lys Met Val Pro Ser Phe Cys Ser Asp Ala
            825                 830                 835
gag gac att gac tgc aga ctg gag gag aac ctg acc aaa aaa tat tgc     3559
Glu Asp Ile Asp Cys Arg Leu Glu Glu Asn Leu Thr Lys Lys Tyr Cys
        840                 845                 850
cta gaa tat aat tat gac tat gaa aat ggc ttt gca att gga cca ggt     3607
Leu Glu Tyr Asn Tyr Asp Tyr Glu Asn Gly Phe Ala Ile Gly Pro Gly
    855                 860                 865
ggc tgg ggt gca gct aat agg ctg gat tac tct tac gat gac ttc ctg     3655
Gly Trp Gly Ala Ala Asn Arg Leu Asp Tyr Ser Tyr Asp Asp Phe Leu
870                 875                 880                 885
gac act gtg caa gaa aca gcc aca agc atc ggc aat gcc aag tcc tca     3703
Asp Thr Val Gln Glu Thr Ala Thr Ser Ile Gly Asn Ala Lys Ser Ser
                890                 895                 900
cgg att aaa aga agt gcc cca tta tct gac tat aaa att aag tta att     3751
Arg Ile Lys Arg Ser Ala Pro Leu Ser Asp Tyr Lys Ile Lys Leu Ile
            905                 910                 915
ttt aac atc aca gct agt gtg cca tta ccc gat gaa aga aat gat acc     3799
Phe Asn Ile Thr Ala Ser Val Pro Leu Pro Asp Glu Arg Asn Asp Thr
        920                 925                 930
ctt gaa tgg gaa aat cag caa cga ctc ctt cag aca ttg gaa act atc     3847
Leu Glu Trp Glu Asn Gln Gln Arg Leu Leu Gln Thr Leu Glu Thr Ile
    935                 940                 945
aca aat aaa ctg aaa agg act ctc aac aaa gac ccc atg tat tcc ttt     3895
Thr Asn Lys Leu Lys Arg Thr Leu Asn Lys Asp Pro Met Tyr Ser Phe
950                 955                 960                 965
cag ctt gca tca gaa ata ctt ata gcc gac agc aat tca tta gaa aca     3943
Gln Leu Ala Ser Glu Ile Leu Ile Ala Asp Ser Asn Ser Leu Glu Thr
                970                 975                 980
aaa aag gct tcc ccc ttc tgc aga cca ggc tca gtg ctg aga ggg cgt     3991
Lys Lys Ala Ser Pro Phe Cys Arg Pro Gly Ser Val Leu Arg Gly Arg
            985                 990                 995
atg tgt gtc  aat tgc cct ttg gga  acc tat tat aat ctg  gaa cat      4036
Met Cys Val  Asn Cys Pro Leu Gly  Thr Tyr Tyr Asn Leu  Glu His
        1000                1005                1010
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ttc acc tgt  gaa agc tgc cgg atc  gga tcc tat caa gat  gaa gaa      4081
Phe Thr Cys  Glu Ser Cys Arg Ile  Gly Ser Tyr Gln Asp  Glu Glu
        1015                 1020                 1025
ggg caa ctt  gag tgc aag ctt tgc  ccc tct ggg atg tac  acg gaa      4126
Gly Gln Leu  Glu Cys Lys Leu Cys  Pro Ser Gly Met Tyr  Thr Glu
        1030                 1035                 1040
tat atc cat  tca aga aac atc tct  gat tgt aaa gct cag  tgt aaa      4171
Tyr Ile His  Ser Arg Asn Ile Ser  Asp Cys Lys Ala Gln  Cys Lys
        1045                 1050                 1055
caa ggc acc  tac tca tac agt gga  ctt gag act tgt gaa  tcg tgt      4216
Gln Gly Thr  Tyr Ser Tyr Ser Gly  Leu Glu Thr Cys Glu  Ser Cys
        1060                 1065                 1070
cca ctg ggc  act tat cag cca aaa  ttt ggt tcc cgg agc  tgc ctc      4261
Pro Leu Gly  Thr Tyr Gln Pro Lys  Phe Gly Ser Arg Ser  Cys Leu
        1075                 1080                 1085
tcg tgt cca  gaa aac acc tca act  gtg aaa aga gga gcc  gtg aac      4306
Ser Cys Pro  Glu Asn Thr Ser Thr  Val Lys Arg Gly Ala  Val Asn
        1090                 1095                 1100
att tct gca  tgt gga gtt cct tgt  cca gaa gga aaa ttc  tcg cgt      4351
Ile Ser Ala  Cys Gly Val Pro Cys  Pro Glu Gly Lys Phe  Ser Arg
        1105                 1110                 1115
tct ggg tta  atg ccc tgt cac cca  tgt cct cgt gac tat  tac caa      4396
Ser Gly Leu  Met Pro Cys His Pro  Cys Pro Arg Asp Tyr  Tyr Gln
        1120                 1125                 1130
cct aat gca  ggg aag gcc ttc tgc  ctg gcc tgt ccc ttt  tat gga      4441
Pro Asn Ala  Gly Lys Ala Phe Cys  Leu Ala Cys Pro Phe  Tyr Gly
        1135                 1140                 1145
act acc cca  ttc gct ggt tcc aga  tcc atc aca gaa tgt  tca agt      4486
Thr Thr Pro  Phe Ala Gly Ser Arg  Ser Ile Thr Glu Cys  Ser Ser
        1150                 1155                 1160
ttt agt tca  act ttc tca gcg gca  gag gaa agt gtg gtg  ccc cct      4531
Phe Ser Ser  Thr Phe Ser Ala Ala  Glu Glu Ser Val Val  Pro Pro
        1165                 1170                 1175
gcc tct ctt  gga cat att aaa aag  agg cat gaa atc agc  agt cag      4576
Ala Ser Leu  Gly His Ile Lys Lys  Arg His Glu Ile Ser  Ser Gln
        1180                 1185                 1190
gtt ttc cat  gaa tgc ttc ttt aac  cct tgc cac aat agt  gga acc      4621
Val Phe His  Glu Cys Phe Phe Asn  Pro Cys His Asn Ser  Gly Thr
        1195                 1200                 1205
tgc cag caa  ctt ggg cgt ggt tat  gtt tgt ctc tgt cca  ctt gga      4666
Cys Gln Gln  Leu Gly Arg Gly Tyr  Val Cys Leu Cys Pro  Leu Gly
        1210                 1215                 1220
tat aca ggc  tta aag tgt gaa aca  gac atc gat gag tgc  agc cca      4711
Tyr Thr Gly  Leu Lys Cys Glu Thr  Asp Ile Asp Glu Cys  Ser Pro
        1225                 1230                 1235
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ctg cct tgc  ctc aac aat gga gtt  tgt aaa gac cta gtt  ggg gaa      4756
Leu Pro Cys  Leu Asn Asn Gly Val  Cys Lys Asp Leu Val  Gly Glu
        1240                 1245                 1250
ttc att tgt  gag tgc cca tca ggt  tac aca ggt cag cgg  tgt gaa      4801
Phe Ile Cys  Glu Cys Pro Ser Gly  Tyr Thr Gly Gln Arg  Cys Glu
        1255                 1260                 1265
gaa aat ata  aat gag tgt agc tcc  agt cct tgt tta aat  aaa gga      4846
Glu Asn Ile  Asn Glu Cys Ser Ser  Ser Pro Cys Leu Asn  Lys Gly
        1270                 1275                 1280
atc tgt gtt  gat ggt gtg gct ggc  tat cgt tgc aca tgt  gtg aaa      4891
Ile Cys Val  Asp Gly Val Ala Gly  Tyr Arg Cys Thr Cys  Val Lys
        1285                 1290                 1295
gga ttt gta  ggc ctg cat tgt gaa  aca gaa gtc aat gaa  tgc cag      4936
Gly Phe Val  Gly Leu His Cys Glu  Thr Glu Val Asn Glu  Cys Gln
        1300                 1305                 1310
tca aac cca  tgc tta aat aat gca  gtc tgt gaa gac cag  gtt ggg      4981
Ser Asn Pro  Cys Leu Asn Asn Ala  Val Cys Glu Asp Gln  Val Gly
        1315                 1320                 1325
gga ttc ttg  tgc aaa tgc cca cct  gga ttt ttg ggt acc  cga tgt      5026
Gly Phe Leu  Cys Lys Cys Pro Pro  Gly Phe Leu Gly Thr  Arg Cys
        1330                 1335                 1340
gga aag aac  gtc gat gag tgt ctc  agt cag cca tgc aaa  aat gga      5071
Gly Lys Asn  Val Asp Glu Cys Leu  Ser Gln Pro Cys Lys  Asn Gly
        1345                 1350                 1355
gct acc tgt  aaa gac ggt gcc aat  agc ttc aga tgc ctg  tgt gca      5116
Ala Thr Cys  Lys Asp Gly Ala Asn  Ser Phe Arg Cys Leu  Cys Ala
        1360                 1365                 1370
gct ggc ttc  aca gga tca cac tgt  gaa ttg aac atc aat  gaa tgt      5161
Ala Gly Phe  Thr Gly Ser His Cys  Glu Leu Asn Ile Asn  Glu Cys
        1375                 1380                 1385
cag tct aat  cca tgt aga aat cag  gcc acc tgt gtg gat  gaa tta      5206
Gln Ser Asn  Pro Cys Arg Asn Gln  Ala Thr Cys Val Asp  Glu Leu
        1390                 1395                 1400
aat tca tac  agt tgt aaa tgt cag  cca gga ttt tca ggc  aaa agg      5251
Asn Ser Tyr  Ser Cys Lys Cys Gln  Pro Gly Phe Ser Gly  Lys Arg
        1405                 1410                 1415
tgt gaa aca  gaa cag tct aca ggc  ttt aac ctg gat ttt  gaa gtt      5296
Cys Glu Thr  Glu Gln Ser Thr Gly  Phe Asn Leu Asp Phe  Glu Val
        1420                 1425                 1430
tct ggc atc  tat gga tat gtc atg  cta gat ggc atg ctc  cca tct      5341
Ser Gly Ile  Tyr Gly Tyr Val Met  Leu Asp Gly Met Leu  Pro Ser
        1435                 1440                 1445
ctc cat gct  cta acc tgt acc ttc  tgg atg aaa tcc tct  gac gac      5386
Leu His Ala  Leu Thr Cys Thr Phe  Trp Met Lys Ser Ser  Asp Asp
        1450                 1455                 1460
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atg aac tat gga aca cca atc tcc tat gca gtt gat aac ggc agc      5431
Met Asn Tyr Gly Thr Pro Ile Ser Tyr Ala Val Asp Asn Gly Ser
      1465                1470                1475
gac aat acc ttg ctc ctg act gat tat aac ggc tgg gtt ctt tat      5476
Asp Asn Thr Leu Leu Leu Thr Asp Tyr Asn Gly Trp Val Leu Tyr
      1480                1485                1490
gtg aat ggc agg gaa aag ata aca aac tgt ccc tcg gtg aat gat      5521
Val Asn Gly Arg Glu Lys Ile Thr Asn Cys Pro Ser Val Asn Asp
      1495                1500                1505
ggc aga tgg cat cat att gca atc act tgg aca agt gcc aat ggc      5566
Gly Arg Trp His His Ile Ala Ile Thr Trp Thr Ser Ala Asn Gly
      1510                1515                1520
atc tgg aaa gtc tat atc gat ggg aaa tta tct gac ggt ggt gct      5611
Ile Trp Lys Val Tyr Ile Asp Gly Lys Leu Ser Asp Gly Gly Ala
      1525                1530                1535
ggc ctc tct gtt ggt ttg ccc ata cct ggt ggt ggt gcg tta gtt      5656
Gly Leu Ser Val Gly Leu Pro Ile Pro Gly Gly Gly Ala Leu Val
      1540                1545                1550
ctg ggg caa gag caa gac aaa aaa gga gag gga ttc agc cca gct      5701
Leu Gly Gln Glu Gln Asp Lys Lys Gly Glu Gly Phe Ser Pro Ala
      1555                1560                1565
gag tct ttt gtg ggc tcc ata agc cag ctc aac ctc tgg gac tat      5746
Glu Ser Phe Val Gly Ser Ile Ser Gln Leu Asn Leu Trp Asp Tyr
      1570                1575                1580
gtc ctg tct cca cag cag gtg aag tca ctg gct acc tcc tgc cca      5791
Val Leu Ser Pro Gln Gln Val Lys Ser Leu Ala Thr Ser Cys Pro
      1585                1590                1595
gag gaa ctc agt aaa gga aac gtg tta gca tgg cct gat ttc ttg      5836
Glu Glu Leu Ser Lys Gly Asn Val Leu Ala Trp Pro Asp Phe Leu
      1600                1605                1610
tca gga att gtg ggg aaa gtg aag atc gat tct aag agc ata ttt      5881
Ser Gly Ile Val Gly Lys Val Lys Ile Asp Ser Lys Ser Ile Phe
      1615                1620                1625
tgt tct gat tgc cca cgc tta gga ggg tca gtg cct cat ctg aga      5926
Cys Ser Asp Cys Pro Arg Leu Gly Gly Ser Val Pro His Leu Arg
      1630                1635                1640
act gca tct gaa gat tta aag cca ggt tcc aaa gtc aat ctg ttc      5971
Thr Ala Ser Glu Asp Leu Lys Pro Gly Ser Lys Val Asn Leu Phe
      1645                1650                1655
tgt gat cca ggc ttc cag ctg gtc ggg aac cct gtg cag tac tgt      6016
Cys Asp Pro Gly Phe Gln Leu Val Gly Asn Pro Val Gln Tyr Cys
      1660                1665                1670
ctg aat caa gga cag tgg aca caa cca ctt cct cac tgt gaa cgc      6061
Leu Asn Gln Gly Gln Trp Thr Gln Pro Leu Pro His Cys Glu Arg
      1675                1680                1685
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att agc tgt ggg gtg cca cct cct ttg gag aat ggc ttc cat tca 6106
Ile Ser Cys Gly Val Pro Pro Pro Leu Glu Asn Gly Phe His Ser
1690 1695 1700
gcc gat gac ttc tat gct ggc agc aca gta acc tac cag tgc aac 6151
Ala Asp Asp Phe Tyr Ala Gly Ser Thr Val Thr Tyr Gln Cys Asn
1705 1710 1715
aat ggc tac tat cta ttg ggt gac tca agg atg ttc tgt aca gat 6196
Asn Gly Tyr Tyr Leu Leu Gly Asp Ser Arg Met Phe Cys Thr Asp
1720 1725 1730
aat ggg agc tgg aac ggc gtt tca cca tcc tgc ctt gat gtc gat 6241
Asn Gly Ser Trp Asn Gly Val Ser Pro Ser Cys Leu Asp Val Asp
1735 1740 1745
gag tgt gca gtt gga tca gat tgt agt gag cat gct tct tgc ctg 6286
Glu Cys Ala Val Gly Ser Asp Cys Ser Glu His Ala Ser Cys Leu
1750 1755 1760
aac gta gat gga tcc tac ata tgt tca tgt gtc cca ccg tac aca 6331
Asn Val Asp Gly Ser Tyr Ile Cys Ser Cys Val Pro Pro Tyr Thr
1765 1770 1775
gga gat ggg aaa aac tgt gca gaa cct ata aaa tgt aag gct cca 6376
Gly Asp Gly Lys Asn Cys Ala Glu Pro Ile Lys Cys Lys Ala Pro
1780 1785 1790
gga aat ccg gaa aat ggc cac tcc tca ggt gag att tat aca gta 6421
Gly Asn Pro Glu Asn Gly His Ser Ser Gly Glu Ile Tyr Thr Val
1795 1800 1805
ggt gcc gca gtc aca ttt tcg tgt cag gaa gga tac cag ttg atg 6466
Gly Ala Ala Val Thr Phe Ser Cys Gln Glu Gly Tyr Gln Leu Met
1810 1815 1820
gga gta acc aaa atc aca tgt ttg gag tct gga gaa tgg aat cat 6511
Gly Val Thr Lys Ile Thr Cys Leu Glu Ser Gly Glu Trp Asn His
1825 1830 1835
cta ata cca tat tgt aaa gct gtt tca tgt ggt aaa ccg gct att 6556
Leu Ile Pro Tyr Cys Lys Ala Val Ser Cys Gly Lys Pro Ala Ile
1840 1845 1850
cca gaa aat ggt tgc att gag gag tta gca ttt act ttt ggc agc 6601
Pro Glu Asn Gly Cys Ile Glu Glu Leu Ala Phe Thr Phe Gly Ser
1855 1860 1865
aaa gtg aca tat agg tgt aat aaa gga tat act ctg gcc ggt gat 6646
Lys Val Thr Tyr Arg Cys Asn Lys Gly Tyr Thr Leu Ala Gly Asp
1870 1875 1880
aaa gaa tca tcc tgt ctt gct aac agt tct tgg agt cat tcc cct 6691
Lys Glu Ser Ser Cys Leu Ala Asn Ser Ser Trp Ser His Ser Pro
1885 1890 1895
cct gtg tgt gaa cca gtg aag tgt tct agt ccg gaa aat ata aat 6736
Pro Val Cys Glu Pro Val Lys Cys Ser Ser Pro Glu Asn Ile Asn
1900 1905 1910

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aat gga aaa  tat att ttg agt ggg  ctt acc tac ctt tct  act gca      6781
Asn Gly Lys  Tyr Ile Leu Ser Gly  Leu Thr Tyr Leu Ser  Thr Ala
        1915                 1920                 1925
tca tat tca  tgc gat aca gga tac  agc tta cag ggc cct  tcc att      6826
Ser Tyr Ser  Cys Asp Thr Gly Tyr  Ser Leu Gln Gly Pro  Ser Ile
        1930                 1935                 1940
att gaa tgc  acg gct tct ggc atc  tgg gac aga gcg cca  cct gcc      6871
Ile Glu Cys  Thr Ala Ser Gly Ile  Trp Asp Arg Ala Pro  Pro Ala
        1945                 1950                 1955
tgt cac ctc  gtc ttc tgt gga gaa  cca cct gcc atc aaa  gat gct      6916
Cys His Leu  Val Phe Cys Gly Glu  Pro Pro Ala Ile Lys  Asp Ala
        1960                 1965                 1970
gtc att acg  ggg aat aac ttc act  ttc agg aac acc gtc  act tac      6961
Val Ile Thr  Gly Asn Asn Phe Thr  Phe Arg Asn Thr Val  Thr Tyr
        1975                 1980                 1985
act tgc aaa  gaa ggc tat act ctt  gct ggt ctt gac acc  att gaa      7006
Thr Cys Lys  Glu Gly Tyr Thr Leu  Ala Gly Leu Asp Thr  Ile Glu
        1990                 1995                 2000
tgc ctg gcc  gac ggc aag tgg agt  aga agt gac cag cag  tgc ctg      7051
Cys Leu Ala  Asp Gly Lys Trp Ser  Arg Ser Asp Gln Gln  Cys Leu
        2005                 2010                 2015
gct gtc tcc  tgt gat gag cca ccc  att gtg gac cac gcc  tct cca      7096
Ala Val Ser  Cys Asp Glu Pro Pro  Ile Val Asp His Ala  Ser Pro
        2020                 2025                 2030
gag act gcc  cat cgg ctc ttt gga  gac att gca ttc tac  tac tgc      7141
Glu Thr Ala  His Arg Leu Phe Gly  Asp Ile Ala Phe Tyr  Tyr Cys
        2035                 2040                 2045
tct gat ggt  tac agc cta gca gac  aat tcc cag ctt ctc  tgc aat      7186
Ser Asp Gly  Tyr Ser Leu Ala Asp  Asn Ser Gln Leu Leu  Cys Asn
        2050                 2055                 2060
gcc cag ggc  aag tgg gta ccc cca  gaa ggt caa gac atg  ccc cgt      7231
Ala Gln Gly  Lys Trp Val Pro Pro  Glu Gly Gln Asp Met  Pro Arg
        2065                 2070                 2075
tgt ata gct  cat ttc tgt gaa aaa  cct cca tcg gtt tcc  tat agc      7276
Cys Ile Ala  His Phe Cys Glu Lys  Pro Pro Ser Val Ser  Tyr Ser
        2080                 2085                 2090
atc ttg gaa  tct gtg agc aaa gca  aaa ttt gca gct ggc  tca gtt      7321
Ile Leu Glu  Ser Val Ser Lys Ala  Lys Phe Ala Ala Gly  Ser Val
        2095                 2100                 2105
gtg agc ttt  aaa tgc atg gaa ggc  ttt gta ctg aac acc  tca gca      7366
Val Ser Phe  Lys Cys Met Glu Gly  Phe Val Leu Asn Thr  Ser Ala
        2110                 2115                 2120
aag att gaa  tgt atg aga ggt ggg  cag tgg aac cct tcc  ccc atg      7411
Lys Ile Glu  Cys Met Arg Gly Gly  Gln Trp Asn Pro Ser  Pro Met
        2125                 2130                 2135
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tcc atc cag  tgc atc cct gtg cgg  tgt gga gag cca cca  agc atc      7456
Ser Ile Gln  Cys Ile Pro Val Arg  Cys Gly Glu Pro Pro  Ser Ile
        2140                 2145                 2150
atg aat ggc  tat gca agt gga tca  aac tac agt ttt gga  gcc atg      7501
Met Asn Gly  Tyr Ala Ser Gly Ser  Asn Tyr Ser Phe Gly  Ala Met
        2155                 2160                 2165
gtg gct tac  agc tgc aac aag ggg  ttc tac atc aaa ggg  gaa aag      7546
Val Ala Tyr  Ser Cys Asn Lys Gly  Phe Tyr Ile Lys Gly  Glu Lys
        2170                 2175                 2180
aag agc acc  tgc gaa gcc aca ggg  cag tgg agt agt cct  ata ccg      7591
Lys Ser Thr  Cys Glu Ala Thr Gly  Gln Trp Ser Ser Pro  Ile Pro
        2185                 2190                 2195
acg tgc cac  ccg gta tct tgt ggt  gaa cca cct aag gtt  gag aat      7636
Thr Cys His  Pro Val Ser Cys Gly  Glu Pro Pro Lys Val  Glu Asn
        2200                 2205                 2210
ggc ttt ctg  gag cat aca act ggc  agg atc ttt gag agt  gaa gtg      7681
Gly Phe Leu  Glu His Thr Thr Gly  Arg Ile Phe Glu Ser  Glu Val
        2215                 2220                 2225
agg tat cag  tgt aac ccg ggc tat  aag tca gtc gga agt  cct gta      7726
Arg Tyr Gln  Cys Asn Pro Gly Tyr  Lys Ser Val Gly Ser  Pro Val
        2230                 2235                 2240
ttt gtc tgc  caa gcc aat cgc cac  tgg cac agt gaa tcc  cct ctg      7771
Phe Val Cys  Gln Ala Asn Arg His  Trp His Ser Glu Ser  Pro Leu
        2245                 2250                 2255
atg tgt gtt  cct ctc gac tgt gga  aaa cct ccc ccg atc  cag aat      7816
Met Cys Val  Pro Leu Asp Cys Gly  Lys Pro Pro Pro Ile  Gln Asn
        2260                 2265                 2270
ggc ttc atg  aaa gga gaa aac ttt  gaa gta ggg tcc aag  gtt cag      7861
Gly Phe Met  Lys Gly Glu Asn Phe  Glu Val Gly Ser Lys  Val Gln
        2275                 2280                 2285
ttt ttc tgt  aat gag ggt tat gag  ctt gtt ggt gac agt  tct tgg      7906
Phe Phe Cys  Asn Glu Gly Tyr Glu  Leu Val Gly Asp Ser  Ser Trp
        2290                 2295                 2300
aca tgt cag  aaa tct ggc aaa tgg  aat aag aag tca aat  cca aag      7951
Thr Cys Gln  Lys Ser Gly Lys Trp  Asn Lys Lys Ser Asn  Pro Lys
        2305                 2310                 2315
tgc atg cct  gcc aag tgc cca gag  ccg ccc ctc ttg gaa  aac cag      7996
Cys Met Pro  Ala Lys Cys Pro Glu  Pro Pro Leu Leu Glu  Asn Gln
        2320                 2325                 2330
cta gta tta  aag gag ttg acc acc  gag gta gga gtt gtg  aca ttt      8041
Leu Val Leu  Lys Glu Leu Thr Thr  Glu Val Gly Val Val  Thr Phe
        2335                 2340                 2345
tcc tgt aaa  gaa ggg cat gtc ctg  caa ggc ccc tct gtc  ctg aaa      8086
Ser Cys Lys  Glu Gly His Val Leu  Gln Gly Pro Ser Val  Leu Lys
        2350                 2355                 2360
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tgc ttg cca  tcc cag caa tgg aat  gac tct ttc cct gtt  tgt aag      8131
Cys Leu Pro  Ser Gln Gln Trp Asn  Asp Ser Phe Pro Val  Cys Lys
        2365                 2370                 2375
att gtt ctt  tgt acc cca cct ccc  cta att tcc ttt ggt  gtc ccc      8176
Ile Val Leu  Cys Thr Pro Pro Pro  Leu Ile Ser Phe Gly  Val Pro
        2380                 2385                 2390
att cct tct  tct gct ctt cat ttt  gga agt act gtc aag  tat tct      8221
Ile Pro Ser  Ser Ala Leu His Phe  Gly Ser Thr Val Lys  Tyr Ser
        2395                 2400                 2405
tgt gta ggt  ggg ttt ttc cta aga  gga aat tct acc acc  ctc tgc      8266
Cys Val Gly  Gly Phe Phe Leu Arg  Gly Asn Ser Thr Thr  Leu Cys
        2410                 2415                 2420
caa cct gat  ggc acc tgg agc tct  cca ctg cca gaa tgt  gtt cca      8311
Gln Pro Asp  Gly Thr Trp Ser Ser  Pro Leu Pro Glu Cys  Val Pro
        2425                 2430                 2435
gta gaa tgt  ccc caa cct gag gaa  atc ccc aat gga atc  att gat      8356
Val Glu Cys  Pro Gln Pro Glu Glu  Ile Pro Asn Gly Ile  Ile Asp
        2440                 2445                 2450
gtg caa ggc  ctt gcc tat ctc agc  aca gct ctc tat acc  tgc aag      8401
Val Gln Gly  Leu Ala Tyr Leu Ser  Thr Ala Leu Tyr Thr  Cys Lys
        2455                 2460                 2465
cca ggc ttt  gaa ttg gtg gga aat  act acc acc ctt tgt  gga gaa      8446
Pro Gly Phe  Glu Leu Val Gly Asn  Thr Thr Thr Leu Cys  Gly Glu
        2470                 2475                 2480
aat ggt cac  tgg ctt gga gga aaa  cca aca tgt aaa gcc  att gag      8491
Asn Gly His  Trp Leu Gly Gly Lys  Pro Thr Cys Lys Ala  Ile Glu
        2485                 2490                 2495
tgc ctg aaa  ccc aag gag att ttg  aat ggc aaa ttc tct  tac acg      8536
Cys Leu Lys  Pro Lys Glu Ile Leu  Asn Gly Lys Phe Ser  Tyr Thr
        2500                 2505                 2510
gac cta cac  tat gga cag acc gtt  acc tac tct tgc aac  cga ggc      8581
Asp Leu His  Tyr Gly Gln Thr Val  Thr Tyr Ser Cys Asn  Arg Gly
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ttt cgg ctc  gaa ggt ccc agt gcc  ttg acc tgt tta gag  aca ggt      8626
Phe Arg Leu  Glu Gly Pro Ser Ala  Leu Thr Cys Leu Glu  Thr Gly
        2530                 2535                 2540
gat tgg gat  gta gat gcc cca tct  tgc aat gcc atc cac  tgt gat      8671
Asp Trp Asp  Val Asp Ala Pro Ser  Cys Asn Ala Ile His  Cys Asp
        2545                 2550                 2555
tcc cca caa  ccc att gaa aat ggt  ttt gta gaa ggt gca  gat tac      8716
Ser Pro Gln  Pro Ile Glu Asn Gly  Phe Val Glu Gly Ala  Asp Tyr
        2560                 2565                 2570
agc tat ggt  gcc ata atc atc tac  agt tgc ttc cct ggg  ttt cag      8761
Ser Tyr Gly  Ala Ile Ile Ile Tyr  Ser Cys Phe Pro Gly  Phe Gln
        2575                 2580                 2585
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gtg gct ggt  cat gcc atg cag acc  tgt gaa gag tca gga  tgg tca      8806
Val Ala Gly  His Ala Met Gln Thr  Cys Glu Glu Ser Gly  Trp Ser
        2590                 2595                 2600
agt tcc atc  cca aca tgt atg cca  ata gac tgt ggc ctc  cct cct      8851
Ser Ser Ile  Pro Thr Cys Met Pro  Ile Asp Cys Gly Leu  Pro Pro
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cat ata gat  ttt gga gac tgt act  aaa ctc aaa gat gac  cag gga      8896
His Ile Asp  Phe Gly Asp Cys Thr  Lys Leu Lys Asp Asp  Gln Gly
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tat ttt gag  caa gaa gac gac atg  atg gaa gtt cca tat  gtg act      8941
Tyr Phe Glu  Gln Glu Asp Asp Met  Met Glu Val Pro Tyr  Val Thr
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cct cac cct  cct tat cat ttg gga  gca gtg gct aaa acc  tgg gaa      8986
Pro His Pro  Pro Tyr His Leu Gly  Ala Val Ala Lys Thr  Trp Glu
        2650                 2655                 2660
aat aca aag  gag tct cct gct aca  cat tca tca aac ttt  ctg tat      9031
Asn Thr Lys  Glu Ser Pro Ala Thr  His Ser Ser Asn Phe  Leu Tyr
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ggt acc atg  gtt tca tac acc tgt  aat cca gga tat gaa  ctt ctg      9076
Gly Thr Met  Val Ser Tyr Thr Cys  Asn Pro Gly Tyr Glu  Leu Leu
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Gly Asn Pro  Val Leu Ile Cys Gln  Glu Asp Gly Thr Trp  Asn Gly
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Ser Ala Pro  Ser Cys Ile Ser Ile  Glu Cys Asp Leu Pro  Thr Ala
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cct gaa aat  ggc ttt ttg cgt ttt  aca gag act agc atg  gga agt      9211
Pro Glu Asn  Gly Phe Leu Arg Phe  Thr Glu Thr Ser Met  Gly Ser
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gct gtg cag  tat agc tgt aaa cct  gga cac att cta gca  ggc tct      9256
Ala Val Gln  Tyr Ser Cys Lys Pro  Gly His Ile Leu Ala  Gly Ser
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gac tta agg  ctt tgt cta gag aat  aga aag tgg agt ggt  gcc tcc      9301
Asp Leu Arg  Leu Cys Leu Glu Asn  Arg Lys Trp Ser Gly  Ala Ser
        2755                 2760                 2765
cca cgc tgt  gaa gcc att tca tgc  aaa aag cca aat cca  gtc atg      9346
Pro Arg Cys  Glu Ala Ile Ser Cys  Lys Lys Pro Asn Pro  Val Met
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aat gga tcc  atc aaa gga agc aac  tac aca tac ctg agc  acg ttg      9391
Asn Gly Ser  Ile Lys Gly Ser Asn  Tyr Thr Tyr Leu Ser  Thr Leu
        2785                 2790                 2795
tac tat gag  tgt gac ccc gga tat  gtg ctg aat ggc act  gag agg      9436
Tyr Tyr Glu  Cys Asp Pro Gly Tyr  Val Leu Asn Gly Thr  Glu Arg
        2800                 2805                 2810
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aga aca tgc  cag gat gac aaa aac  tgg gat gag gat gag  ccc att      9481
Arg Thr Cys  Gln Asp Asp Lys Asn  Trp Asp Glu Asp Glu  Pro Ile
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tgc att cct  gtg gac tgc agt tca  ccc cca gtc tca gcc  aat ggc      9526
Cys Ile Pro  Val Asp Cys Ser Ser  Pro Pro Val Ser Ala  Asn Gly
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cag gtg aga  gga gac gag tac aca  ttc caa aaa gag att  gaa tac      9571
Gln Val Arg  Gly Asp Glu Tyr Thr  Phe Gln Lys Glu Ile  Glu Tyr
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Thr Cys Asn  Glu Gly Phe Leu Leu  Glu Gly Ala Arg Ser  Arg Val
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tgt ctt gcc  aat gga agt tgg agt  gga gcc act ccc gac  tgt gtg      9661
Cys Leu Ala  Asn Gly Ser Trp Ser  Gly Ala Thr Pro Asp  Cys Val
        2875                 2880                 2885
cct gtc aga  tgt gcc acc ccg cca  caa ctg gcc aat ggg  gtg acg      9706
Pro Val Arg  Cys Ala Thr Pro Pro  Gln Leu Ala Asn Gly  Val Thr
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gaa ggc ctg  gac tat ggc ttc atg  aag gaa gta aca ttc  cac tgt      9751
Glu Gly Leu  Asp Tyr Gly Phe Met  Lys Glu Val Thr Phe  His Cys
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cac gag ggc  tac atc ttg cac ggt  gct cca aaa ctc acc  tgt cag      9796
His Glu Gly  Tyr Ile Leu His Gly  Ala Pro Lys Leu Thr  Cys Gln
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Ser Asp Gly  Asn Trp Asp Ala Glu  Ile Pro Leu Cys Lys  Pro Val
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Asn Cys Gly  Pro Pro Glu Asp Leu  Ala His Gly Phe Pro  Asn Gly
        2950                 2955                 2960
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Phe Ser Phe  Ile His Gly Gly His  Ile Gln Tyr Gln Cys  Phe Pro
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ggt tat aag  ctc cat gga aat tca  tca aga agg tgc ctc  tcc aat      9976
Gly Tyr Lys  Leu His Gly Asn Ser  Ser Arg Arg Cys Leu  Ser Asn
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Gly Ser Trp  Ser Gly Ser Ser Pro  Ser Cys Leu Pro Cys  Arg Cys
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tcc aca cca  gta att gaa tat gga  act gtc aat ggg aca  gat ttt     10066
Ser Thr Pro  Val Ile Glu Tyr Gly  Thr Val Asn Gly Thr  Asp Phe
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gac tgt gga  aag gca gcc cgg att  cag tgc ttc aaa ggc  ttc aag     10111
Asp Cys Gly  Lys Ala Ala Arg Ile  Gln Cys Phe Lys Gly  Phe Lys
        3025                 3030                 3035
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Leu Leu Gly  Leu Ser Glu Ile Thr  Cys Glu Ala Asp Gly  Gln Trp
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agc tct ggg  ttc ccc cac tgt gaa  cac act tct tgt ggt  tct ctt     10201
Ser Ser Gly  Phe Pro His Cys Glu  His Thr Ser Cys Gly  Ser Leu
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cca atg ata  cca aat gcg ttc atc  agt gag acc agc tct  tgg aag     10246
Pro Met Ile  Pro Asn Ala Phe Ile  Ser Glu Thr Ser Ser  Trp Lys
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gaa aat gtg  ata act tac agc tgc  agg tct gga tat gtc  ata caa     10291
Glu Asn Val  Ile Thr Tyr Ser Cys  Arg Ser Gly Tyr Val  Ile Gln
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Gly Ser Ser  Asp Leu Ile Cys Thr  Glu Lys Gly Val Trp  Ser Gln
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cct tat cca  gtc tgt gag ccc ttg  tcc tgt ggg tcc cca  ccg tct     10381
Pro Tyr Pro  Val Cys Glu Pro Leu  Ser Cys Gly Ser Pro  Pro Ser
        3115                 3120                 3125
gtc gcc aat  gca gtg gca act gga  gag gca cac acc tat  gaa agt     10426
Val Ala Asn  Ala Val Ala Thr Gly  Glu Ala His Thr Tyr  Glu Ser
        3130                 3135                 3140
gaa gtg aaa  ctc aga tgt ctg gaa  ggt tat acg atg gat  aca gat     10471
Glu Val Lys  Leu Arg Cys Leu Glu  Gly Tyr Thr Met Asp  Thr Asp
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aca gat aca  ttc acc tgt cag aaa  gat ggt cgc tgg ttc  cct gag     10516
Thr Asp Thr  Phe Thr Cys Gln Lys  Asp Gly Arg Trp Phe  Pro Glu
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aga atc tcc  tgc agt cct aaa aaa  tgt cct ctc ccg gaa  aac ata     10561
Arg Ile Ser  Cys Ser Pro Lys Lys  Cys Pro Leu Pro Glu  Asn Ile
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Thr His Ile  Leu Val His Gly Asp  Asp Phe Ser Val Asn  Arg Gln
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gtt tct gtg  tca tgt gca gaa ggg  tat acc ttt gag gga  gtt aac     10651
Val Ser Val  Ser Cys Ala Glu Gly  Tyr Thr Phe Glu Gly  Val Asn
        3205                 3210                 3215
ata tca gta  tgt cag ctt gat gga  acc tgg gag cca cca  ttc tcc     10696
Ile Ser Val  Cys Gln Leu Asp Gly  Thr Trp Glu Pro Pro  Phe Ser
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Asp Glu Ser  Cys Ser Pro Val Ser  Cys Gly Lys Pro Glu  Ser Pro
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gaa cat gga  ttt gtg gtt ggc agt  aaa tac acc ttt gaa  agc aca     10786
Glu His Gly  Phe Val Val Gly Ser  Lys Tyr Thr Phe Glu  Ser Thr
        3250                 3255                 3260
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Ile Ile Tyr  Gln Cys Glu Pro Gly  Tyr Glu Leu Glu Gly  Asn Arg
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gaa cgt gtc  tgc cag gag aac aga  cag tgg agt gga ggg  gtg gca     10876
Glu Arg Val  Cys Gln Glu Asn Arg  Gln Trp Ser Gly Gly  Val Ala
        3280                 3285                 3290
ata tgc aaa  gag acc agg tgt gaa  act cca ctt gaa ttt  ctc aat     10921
Ile Cys Lys  Glu Thr Arg Cys Glu  Thr Pro Leu Glu Phe  Leu Asn
        3295                 3300                 3305
ggg aaa gct  gac att gaa aac agg  acg act gga ccc aac  gtg gta     10966
Gly Lys Ala  Asp Ile Glu Asn Arg  Thr Thr Gly Pro Asn  Val Val
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tat tcc tgc  aac aga ggc tac agt  ctt gaa ggg cca tct  gag gca     11011
Tyr Ser Cys  Asn Arg Gly Tyr Ser  Leu Glu Gly Pro Ser  Glu Ala
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cac tgc aca  gaa aat gga acc tgg  agc cac cca gtc cct  ctc tgc     11056
His Cys Thr  Glu Asn Gly Thr Trp  Ser His Pro Val Pro  Leu Cys
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Lys Pro Asn  Pro Cys Pro Val Pro  Phe Val Ile Pro Glu  Asn Ala
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ctg ctg tct  gaa aag gag ttt tat  gtt gat cag aat gtg  tcc atc     11146
Leu Leu Ser  Glu Lys Glu Phe Tyr  Val Asp Gln Asn Val  Ser Ile
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aaa tgt agg  gaa ggt ttt ctg ctg  cag ggc cac ggc atc  att acc     11191
Lys Cys Arg  Glu Gly Phe Leu Leu  Gln Gly His Gly Ile  Ile Thr
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tgc aac ccc  gac gag acg tgg aca  cag aca agc gcc aaa  tgt gaa     11236
Cys Asn Pro  Asp Glu Thr Trp Thr  Gln Thr Ser Ala Lys  Cys Glu
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aaa atc tca  tgt ggt cca cca gct  cac gta gaa aat gca  att gct     11281
Lys Ile Ser  Cys Gly Pro Pro Ala  His Val Glu Asn Ala  Ile Ala
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cga ggc gta  cat tat caa tat gga  gac atg atc acc tac  tca tgt     11326
Arg Gly Val  His Tyr Gln Tyr Gly  Asp Met Ile Thr Tyr  Ser Cys
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Tyr Ser Gly  Tyr Met Leu Glu Gly  Phe Leu Arg Ser Val  Cys Leu
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gaa aat gga  aca tgg aca tca cct  cct att tgc aga gct  gtc tgt     11416
Glu Asn Gly  Thr Trp Thr Ser Pro  Pro Ile Cys Arg Ala  Val Cys
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cga ttt cca  tgt cag aat ggg ggc  atc tgc caa cgc cca  aat gct     11461
Arg Phe Pro  Cys Gln Asn Gly Gly  Ile Cys Gln Arg Pro  Asn Ala
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Cys Ser Cys  Pro Glu Gly Trp Met  Gly Arg Leu Cys Glu  Glu Pro
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atc tgc att  ctt ccc tgt ctg aac  gga ggt cgc tgt gtg  gcc cct     11551
Ile Cys Ile  Leu Pro Cys Leu Asn  Gly Gly Arg Cys Val  Ala Pro
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tac cag tgt  gac tgc ccg cct ggc  tgg acg ggg tct cgc  tgt cat     11596
Tyr Gln Cys  Asp Cys Pro Pro Gly  Trp Thr Gly Ser Arg  Cys His
        3520                 3525                 3530
aca gct gtt  tgc cag tct ccc tgc  tta aat ggt gga aaa  tgt gta     11641
Thr Ala Val  Cys Gln Ser Pro Cys  Leu Asn Gly Gly Lys  Cys Val
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aga cca aac  cga tgt cac tgt ctt  tct tct tgg acg gga  cat aac     11686
Arg Pro Asn  Arg Cys His Cys Leu  Ser Ser Trp Thr Gly  His Asn
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tgt tcc agg  aaa agg agg act ggg  ttt taa ccactgcacg accatctggc    11736
Cys Ser Arg  Lys Arg Arg Thr Gly  Phe
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            20                  25                  30
Arg Leu Phe Pro Glu Thr Ala Pro Gly Ala Pro Gly Ser Ile Pro Ala
        35                  40                  45
Pro Pro Ala Pro Gly Asp Glu Ala Ala Gly Ser Arg Val Glu Arg Leu
    50                  55                  60
Gly Gln Ala Phe Arg Arg Arg Val Arg Leu Leu Arg Glu Leu Ser Glu
65                  70                  75                  80
Arg Leu Glu Leu Val Phe Leu Val Asp Asp Ser Ser Ser Val Gly Glu
                85                  90                  95
Val Asn Phe Arg Ser Glu Leu Met Phe Val Arg Lys Leu Leu Ser Asp
            100                 105                 110
Phe Pro Val Val Pro Thr Ala Thr Arg Val Ala Ile Val Thr Phe Ser
        115                 120                 125
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Ser Lys Asn Tyr Val Val Pro Arg Val Asp Tyr Ile Ser Thr Arg Arg
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Ala Arg Gln His Lys Cys Ala Leu Leu Leu Gln Glu Ile Pro Ala Ile
145                 150                 155                 160
Ser Tyr Arg Gly Gly Gly Thr Tyr Thr Lys Gly Ala Phe Gln Gln Ala
                165                 170                 175
Ala Gln Ile Leu Leu His Ala Arg Glu Asn Ser Thr Lys Val Val Phe
            180                 185                 190
Leu Ile Thr Asp Gly Tyr Ser Asn Gly Gly Asp Pro Arg Pro Ile Ala
        195                 200                 205
Ala Ser Leu Arg Asp Ser Gly Val Glu Ile Phe Thr Phe Gly Ile Trp
    210                 215                 220
Gln Gly Asn Ile Arg Glu Leu Asn Asp Met Ala Ser Thr Pro Lys Glu
225                 230                 235                 240
Glu His Cys Tyr Leu Leu His Ser Phe Glu Glu Phe Glu Ala Leu Ala
                245                 250                 255
Arg Arg Ala Leu His Glu Asp Leu Pro Ser Gly Ser Phe Ile Gln Asp
            260                 265                 270
Asp Met Val His Cys Ser Tyr Leu Cys Asp Glu Gly Lys Asp Cys Cys
        275                 280                 285
Asp Arg Met Gly Ser Cys Lys Cys Gly Thr His Thr Gly His Phe Glu
    290                 295                 300
Cys Ile Cys Glu Lys Gly Tyr Tyr Gly Lys Gly Leu Gln Tyr Glu Cys
305                 310                 315                 320
Thr Ala Cys Pro Ser Gly Thr Tyr Lys Pro Glu Gly Ser Pro Gly Gly
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Ile Ser Ser Cys Ile Pro Cys Pro Asp Glu Asn His Thr Ser Pro Pro
            340                 345                 350
Gly Ser Thr Ser Pro Glu Asp Cys Val Cys Arg Glu Gly Tyr Arg Ala
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Ser Gly Gln Thr Cys Glu Leu Val His Cys Pro Ala Leu Lys Pro Pro
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Glu Asn Gly Tyr Phe Ile Gln Asn Thr Cys Asn Asn His Phe Asn Ala
385                 390                 395                 400
Ala Cys Gly Val Arg Cys His Pro Gly Phe Asp Leu Val Gly Ser Ser
                405                 410                 415
Ile Ile Leu Cys Leu Pro Asn Gly Leu Trp Ser Gly Ser Glu Ser Tyr
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Cys Arg Val Arg Thr Cys Pro His Leu Arg Gln Pro Lys His Gly His
        435                 440                 445
Ile Ser Cys Ser Thr Arg Glu Met Leu Tyr Lys Thr Thr Cys Leu Val
    450                 455                 460
Ala Cys Asp Glu Gly Tyr Arg Leu Glu Gly Ser Asp Lys Leu Thr Cys
465                 470                 475                 480
Gln Gly Asn Ser Gln Trp Asp Gly Pro Glu Pro Arg Cys Val Glu Arg
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His Cys Ser Thr Phe Gln Met Pro Lys Asp Val Ile Ile Ser Pro His
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Thr Thr Ser Gly Lys Trp Asn Val Gly Val Gln Ala Ala Val Cys Lys
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Asp Val Glu Ala Pro Gln Ile Asn Cys Pro Lys Asp Ile Glu Ala Lys
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Thr Leu Glu Gln Gln Asp Ser Ala Asn Val Thr Trp Gln Ile Pro Thr
580 585 590
Ala Lys Asp Asn Ser Gly Glu Lys Val Ser Val His Val His Pro Ala
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Phe Thr Pro Pro Tyr Leu Phe Pro Ile Gly Asp Val Ala Ile Val Tyr
610 615 620
Thr Ala Thr Asp Leu Ser Gly Asn Gln Ala Ser Cys Ile Phe His Ile
625 630 635 640
Lys Val Ile Asp Ala Glu Pro Pro Val Ile Asp Trp Cys Arg Ser Pro
645 650 655
Pro Pro Val Gln Val Ser Glu Lys Val His Ala Ala Ser Trp Asp Glu
660 665 670
Pro Gln Phe Ser Asp Asn Ser Gly Ala Glu Leu Val Ile Thr Arg Ser
675 680 685
His Thr Gln Gly Asp Leu Phe Pro Gln Gly Glu Thr Ile Val Gln Tyr
690 695 700
Thr Ala Thr Asp Pro Ser Gly Asn Asn Arg Thr Cys Asp Ile His Ile
705 710 715 720
Val Ile Lys Gly Ser Pro Cys Glu Ile Pro Phe Thr Pro Val Asn Gly
725 730 735
Asp Phe Ile Cys Thr Pro Asp Asn Thr Gly Val Asn Cys Thr Leu Thr
740 745 750
Cys Leu Glu Gly Tyr Asp Phe Thr Glu Gly Ser Thr Asp Lys Tyr Tyr
755 760 765
Cys Ala Tyr Glu Asp Gly Val Trp Lys Pro Thr Tyr Thr Thr Glu Trp
770 775 780
Pro Asp Cys Ala Lys Lys Arg Phe Ala Asn His Gly Phe Lys Ser Phe
785 790 795 800
Glu Met Phe Tyr Lys Ala Ala Arg Cys Asp Asp Thr Asp Leu Met Lys
805 810 815
Lys Phe Ser Glu Ala Phe Glu Thr Thr Leu Gly Lys Met Val Pro Ser
820 825 830
Phe Cys Ser Asp Ala Glu Asp Ile Asp Cys Arg Leu Glu Glu Asn Leu
835 840 845

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Tyr Asp Asp Phe Leu Asp Thr Val Gln Glu Thr Ala Thr Ser Ile Gly
                885                 890                 895
Asn Ala Lys Ser Ser Arg Ile Lys Arg Ser Ala Pro Leu Ser Asp Tyr
            900                 905                 910
Lys Ile Lys Leu Ile Phe Asn Ile Thr Ala Ser Val Pro Leu Pro Asp
        915                 920                 925
Glu Arg Asn Asp Thr Leu Glu Trp Glu Asn Gln Gln Arg Leu Leu Gln
    930                 935                 940
Thr Leu Glu Thr Ile Thr Asn Lys Leu Lys Arg Thr Leu Asn Lys Asp
945                 950                 955                 960
Pro Met Tyr Ser Phe Gln Leu Ala Ser Glu Ile Leu Ile Ala Asp Ser
                965                 970                 975
Asn Ser Leu Glu Thr Lys Lys Ala Ser Pro Phe Cys Arg Pro Gly Ser
            980                 985                 990
Val Leu Arg Gly Arg Met Cys Val  Asn Cys Pro Leu Gly  Thr Tyr Tyr
        995                 1000                1005
Asn Leu  Glu His Phe Thr Cys  Glu Ser Cys Arg Ile  Gly Ser Tyr
    1010                1015                1020
Gln Asp  Glu Glu Gly Gln Leu  Glu Cys Lys Leu Cys  Pro Ser Gly
    1025                1030                1035
Met Tyr  Thr Glu Tyr Ile His  Ser Arg Asn Ile Ser  Asp Cys Lys
    1040                1045                1050
Ala Gln  Cys Lys Gln Gly Thr  Tyr Ser Tyr Ser Gly  Leu Glu Thr
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Cys Glu  Ser Cys Pro Leu Gly  Thr Tyr Gln Pro Lys  Phe Gly Ser
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Arg Ser  Cys Leu Ser Cys Pro  Glu Asn Thr Ser Thr  Val Lys Arg
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Gly Ala  Val Asn Ile Ser Ala  Cys Gly Val Pro Cys  Pro Glu Gly
    1100                1105                1110
Lys Phe  Ser Arg Ser Gly Leu  Met Pro Cys His Pro  Cys Pro Arg
    1115                1120                1125
Asp Tyr  Tyr Gln Pro Asn Ala  Gly Lys Ala Phe Cys  Leu Ala Cys
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Pro Phe  Tyr Gly Thr Thr Pro  Phe Ala Gly Ser Arg  Ser Ile Thr
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Glu Cys  Ser Ser Phe Ser Ser  Thr Phe Ser Ala Ala  Glu Glu Ser
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Val Val  Pro Pro Ala Ser Leu  Gly His Ile Lys Lys  Arg His Glu
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Ile Ser  Ser Gln Val Phe His  Glu Cys Phe Phe Asn  Pro Cys His
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Thr Cys Val Lys Gly Phe Val Gly Leu His Cys Glu Thr Glu Val
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Gly Thr Arg Cys Gly Lys Asn Val Asp Glu Cys Leu Ser Gln Pro
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Cys Lys Asn Gly Ala Thr Cys Lys Asp Gly Ala Asn Ser Phe Arg
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Cys Leu Cys Ala Ala Gly Phe Thr Gly Ser His Cys Glu Leu Asn
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Asp Phe Glu Val Ser Gly Ile Tyr Gly Tyr Val Met Leu Asp Gly
1430 1435 1440
Met Leu Pro Ser Leu His Ala Leu Thr Cys Thr Phe Trp Met Lys
1445 1450 1455
Ser Ser Asp Asp Met Asn Tyr Gly Thr Pro Ile Ser Tyr Ala Val
1460 1465 1470
Asp Asn Gly Ser Asp Asn Thr Leu Leu Leu Thr Asp Tyr Asn Gly
1475 1480 1485
Trp Val Leu Tyr Val Asn Gly Arg Glu Lys Ile Thr Asn Cys Pro
1490 1495 1500
Ser Val Asn Asp Gly Arg Trp His His Ile Ala Ile Thr Trp Thr
1505 1510 1515
Ser Ala Asn Gly Ile Trp Lys Val Tyr Ile Asp Gly Lys Leu Ser
1520 1525 1530

Asp Gly Gly Ala Gly Leu Ser Val Gly Leu Pro Ile Pro Gly Gly
1535 1540 1545
Gly Ala Leu Val Leu Gly Gln Glu Gln Asp Lys Lys Gly Glu Gly
1550 1555 1560
Phe Ser Pro Ala Glu Ser Phe Val Gly Ser Ile Ser Gln Leu Asn
1565 1570 1575
Leu Trp Asp Tyr Val Leu Ser Pro Gln Gln Val Lys Ser Leu Ala
1580 1585 1590
Thr Ser Cys Pro Glu Glu Leu Ser Lys Gly Asn Val Leu Ala Trp
1595 1600 1605
Pro Asp Phe Leu Ser Gly Ile Val Gly Lys Val Lys Ile Asp Ser
1610 1615 1620
Lys Ser Ile Phe Cys Ser Asp Cys Pro Arg Leu Gly Gly Ser Val
1625 1630 1635
Pro His Leu Arg Thr Ala Ser Glu Asp Leu Lys Pro Gly Ser Lys
1640 1645 1650
Val Asn Leu Phe Cys Asp Pro Gly Phe Gln Leu Val Gly Asn Pro
1655 1660 1665
Val Gln Tyr Cys Leu Asn Gln Gly Gln Trp Thr Gln Pro Leu Pro
1670 1675 1680
His Cys Glu Arg Ile Ser Cys Gly Val Pro Pro Pro Leu Glu Asn
1685 1690 1695
Gly Phe His Ser Ala Asp Asp Phe Tyr Ala Gly Ser Thr Val Thr
1700 1705 1710
Tyr Gln Cys Asn Asn Gly Tyr Tyr Leu Leu Gly Asp Ser Arg Met
1715 1720 1725
Phe Cys Thr Asp Asn Gly Ser Trp Asn Gly Val Ser Pro Ser Cys
1730 1735 1740
Leu Asp Val Asp Glu Cys Ala Val Gly Ser Asp Cys Ser Glu His
1745 1750 1755
Ala Ser Cys Leu Asn Val Asp Gly Ser Tyr Ile Cys Ser Cys Val
1760 1765 1770
Pro Pro Tyr Thr Gly Asp Gly Lys Asn Cys Ala Glu Pro Ile Lys
1775 1780 1785
Cys Lys Ala Pro Gly Asn Pro Glu Asn Gly His Ser Ser Gly Glu
1790 1795 1800
Ile Tyr Thr Val Gly Ala Ala Val Thr Phe Ser Cys Gln Glu Gly
1805 1810 1815
Tyr Gln Leu Met Gly Val Thr Lys Ile Thr Cys Leu Glu Ser Gly
1820 1825 1830
Glu Trp Asn His Leu Ile Pro Tyr Cys Lys Ala Val Ser Cys Gly
1835 1840 1845
Lys Pro Ala Ile Pro Glu Asn Gly Cys Ile Glu Glu Leu Ala Phe
1850 1855 1860
Thr Phe Gly Ser Lys Val Thr Tyr Arg Cys Asn Lys Gly Tyr Thr

1865 1870 1875
Leu Ala Gly Asp Lys Glu Ser Ser Cys Leu Ala Asn Ser Ser Trp
1880 1885 1890
Ser His Ser Pro Pro Val Cys Glu Pro Val Lys Cys Ser Ser Pro
1895 1900 1905
Glu Asn Ile Asn Asn Gly Lys Tyr Ile Leu Ser Gly Leu Thr Tyr
1910 1915 1920
Leu Ser Thr Ala Ser Tyr Ser Cys Asp Thr Gly Tyr Ser Leu Gln
1925 1930 1935
Gly Pro Ser Ile Ile Glu Cys Thr Ala Ser Gly Ile Trp Asp Arg
1940 1945 1950
Ala Pro Pro Ala Cys His Leu Val Phe Cys Gly Glu Pro Pro Ala
1955 1960 1965
Ile Lys Asp Ala Val Ile Thr Gly Asn Asn Phe Thr Phe Arg Asn
1970 1975 1980
Thr Val Thr Tyr Thr Cys Lys Glu Gly Tyr Thr Leu Ala Gly Leu
1985 1990 1995
Asp Thr Ile Glu Cys Leu Ala Asp Gly Lys Trp Ser Arg Ser Asp
2000 2005 2010
Gln Gln Cys Leu Ala Val Ser Cys Asp Glu Pro Pro Ile Val Asp
2015 2020 2025
His Ala Ser Pro Glu Thr Ala His Arg Leu Phe Gly Asp Ile Ala
2030 2035 2040
Phe Tyr Tyr Cys Ser Asp Gly Tyr Ser Leu Ala Asp Asn Ser Gln
2045 2050 2055
Leu Leu Cys Asn Ala Gln Gly Lys Trp Val Pro Pro Glu Gly Gln
2060 2065 2070
Asp Met Pro Arg Cys Ile Ala His Phe Cys Glu Lys Pro Pro Ser
2075 2080 2085
Val Ser Tyr Ser Ile Leu Glu Ser Val Ser Lys Ala Lys Phe Ala
2090 2095 2100
Ala Gly Ser Val Val Ser Phe Lys Cys Met Glu Gly Phe Val Leu
2105 2110 2115
Asn Thr Ser Ala Lys Ile Glu Cys Met Arg Gly Gly Gln Trp Asn
2120 2125 2130
Pro Ser Pro Met Ser Ile Gln Cys Ile Pro Val Arg Cys Gly Glu
2135 2140 2145
Pro Pro Ser Ile Met Asn Gly Tyr Ala Ser Gly Ser Asn Tyr Ser
2150 2155 2160
Phe Gly Ala Met Val Ala Tyr Ser Cys Asn Lys Gly Phe Tyr Ile
2165 2170 2175
Lys Gly Glu Lys Lys Ser Thr Cys Glu Ala Thr Gly Gln Trp Ser
2180 2185 2190
Ser Pro Ile Pro Thr Cys His Pro Val Ser Cys Gly Glu Pro Pro
2195 2200 2205

Lys Val Glu Asn Gly Phe Leu Glu His Thr Thr Gly Arg Ile Phe
2210 2215 2220
Glu Ser Glu Val Arg Tyr Gln Cys Asn Pro Gly Tyr Lys Ser Val
2225 2230 2235
Gly Ser Pro Val Phe Val Cys Gln Ala Asn Arg His Trp His Ser
2240 2245 2250
Glu Ser Pro Leu Met Cys Val Pro Leu Asp Cys Gly Lys Pro Pro
2255 2260 2265
Pro Ile Gln Asn Gly Phe Met Lys Gly Glu Asn Phe Glu Val Gly
2270 2275 2280
Ser Lys Val Gln Phe Phe Cys Asn Glu Gly Tyr Glu Leu Val Gly
2285 2290 2295
Asp Ser Ser Trp Thr Cys Gln Lys Ser Gly Lys Trp Asn Lys Lys
2300 2305 2310
Ser Asn Pro Lys Cys Met Pro Ala Lys Cys Pro Glu Pro Pro Leu
2315 2320 2325
Leu Glu Asn Gln Leu Val Leu Lys Glu Leu Thr Thr Glu Val Gly
2330 2335 2340
Val Val Thr Phe Ser Cys Lys Glu Gly His Val Leu Gln Gly Pro
2345 2350 2355
Ser Val Leu Lys Cys Leu Pro Ser Gln Gln Trp Asn Asp Ser Phe
2360 2365 2370
Pro Val Cys Lys Ile Val Leu Cys Thr Pro Pro Pro Leu Ile Ser
2375 2380 2385
Phe Gly Val Pro Ile Pro Ser Ser Ala Leu His Phe Gly Ser Thr
2390 2395 2400
Val Lys Tyr Ser Cys Val Gly Gly Phe Phe Leu Arg Gly Asn Ser
2405 2410 2415
Thr Thr Leu Cys Gln Pro Asp Gly Thr Trp Ser Ser Pro Leu Pro
2420 2425 2430
Glu Cys Val Pro Val Glu Cys Pro Gln Pro Glu Glu Ile Pro Asn
2435 2440 2445
Gly Ile Ile Asp Val Gln Gly Leu Ala Tyr Leu Ser Thr Ala Leu
2450 2455 2460
Tyr Thr Cys Lys Pro Gly Phe Glu Leu Val Gly Asn Thr Thr Thr
2465 2470 2475
Leu Cys Gly Glu Asn Gly His Trp Leu Gly Gly Lys Pro Thr Cys
2480 2485 2490
Lys Ala Ile Glu Cys Leu Lys Pro Lys Glu Ile Leu Asn Gly Lys
2495 2500 2505
Phe Ser Tyr Thr Asp Leu His Tyr Gly Gln Thr Val Thr Tyr Ser
2510 2515 2520
Cys Asn Arg Gly Phe Arg Leu Glu Gly Pro Ser Ala Leu Thr Cys
2525 2530 2535
Leu Glu Thr Gly Asp Trp Asp Val Asp Ala Pro Ser Cys Asn Ala

2540 2545 2550
Ile His Cys Asp Ser Pro Gln Pro Ile Glu Asn Gly Phe Val Glu
2555 2560 2565
Gly Ala Asp Tyr Ser Tyr Gly Ala Ile Ile Ile Tyr Ser Cys Phe
2570 2575 2580
Pro Gly Phe Gln Val Ala Gly His Ala Met Gln Thr Cys Glu Glu
2585 2590 2595
Ser Gly Trp Ser Ser Ser Ile Pro Thr Cys Met Pro Ile Asp Cys
2600 2605 2610
Gly Leu Pro Pro His Ile Asp Phe Gly Asp Cys Thr Lys Leu Lys
2615 2620 2625
Asp Asp Gln Gly Tyr Phe Glu Gln Glu Asp Asp Met Met Glu Val
2630 2635 2640
Pro Tyr Val Thr Pro His Pro Pro Tyr His Leu Gly Ala Val Ala
2645 2650 2655
Lys Thr Trp Glu Asn Thr Lys Glu Ser Pro Ala Thr His Ser Ser
2660 2665 2670
Asn Phe Leu Tyr Gly Thr Met Val Ser Tyr Thr Cys Asn Pro Gly
2675 2680 2685
Tyr Glu Leu Leu Gly Asn Pro Val Leu Ile Cys Gln Glu Asp Gly
2690 2695 2700
Thr Trp Asn Gly Ser Ala Pro Ser Cys Ile Ser Ile Glu Cys Asp
2705 2710 2715
Leu Pro Thr Ala Pro Glu Asn Gly Phe Leu Arg Phe Thr Glu Thr
2720 2725 2730
Ser Met Gly Ser Ala Val Gln Tyr Ser Cys Lys Pro Gly His Ile
2735 2740 2745
Leu Ala Gly Ser Asp Leu Arg Leu Cys Leu Glu Asn Arg Lys Trp
2750 2755 2760
Ser Gly Ala Ser Pro Arg Cys Glu Ala Ile Ser Cys Lys Lys Pro
2765 2770 2775
Asn Pro Val Met Asn Gly Ser Ile Lys Gly Ser Asn Tyr Thr Tyr
2780 2785 2790
Leu Ser Thr Leu Tyr Tyr Glu Cys Asp Pro Gly Tyr Val Leu Asn
2795 2800 2805
Gly Thr Glu Arg Arg Thr Cys Gln Asp Asp Lys Asn Trp Asp Glu
2810 2815 2820
Asp Glu Pro Ile Cys Ile Pro Val Asp Cys Ser Ser Pro Pro Val
2825 2830 2835
Ser Ala Asn Gly Gln Val Arg Gly Asp Glu Tyr Thr Phe Gln Lys
2840 2845 2850
Glu Ile Glu Tyr Thr Cys Asn Glu Gly Phe Leu Leu Glu Gly Ala
2855 2860 2865
Arg Ser Arg Val Cys Leu Ala Asn Gly Ser Trp Ser Gly Ala Thr
2870 2875 2880

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Pro Asp  Cys Val Pro Val Arg  Cys Ala Thr Pro Pro  Gln Leu Ala
2885-                2890                 2895
Asn Gly  Val Thr Glu Gly Leu  Asp Tyr Gly Phe Met  Lys Glu Val
2900                 2905                 2910
Thr Phe  His Cys His Glu Gly  Tyr Ile Leu His Gly  Ala Pro Lys
2915                 2920                 2925
Leu Thr  Cys Gln Ser Asp Gly  Asn Trp Asp Ala Glu  Ile Pro Leu
2930                 2935                 2940
Cys Lys  Pro Val Asn Cys Gly  Pro Pro Glu Asp Leu  Ala His Gly
2945                 2950                 2955
Phe Pro  Asn Gly Phe Ser Phe  Ile His Gly Gly His  Ile Gln Tyr
2960                 2965                 2970
Gln Cys  Phe Pro Gly Tyr Lys  Leu His Gly Asn Ser  Ser Arg Arg
2975                 2980                 2985
Cys Leu  Ser Asn Gly Ser Trp  Ser Gly Ser Ser Pro  Ser Cys Leu
2990                 2995                 3000
Pro Cys  Arg Cys Ser Thr Pro  Val Ile Glu Tyr Gly  Thr Val Asn
3005                 3010                 3015
Gly Thr  Asp Phe Asp Cys Gly  Lys Ala Ala Arg Ile  Gln Cys Phe
3020                 3025                 3030
Lys Gly  Phe Lys Leu Leu Gly  Leu Ser Glu Ile Thr  Cys Glu Ala
3035                 3040                 3045
Asp Gly  Gln Trp Ser Ser Gly  Phe Pro His Cys Glu  His Thr Ser
3050                 3055                 3060
Cys Gly  Ser Leu Pro Met Ile  Pro Asn Ala Phe Ile  Ser Glu Thr
3065                 3070                 3075
Ser Ser  Trp Lys Glu Asn Val  Ile Thr Tyr Ser Cys  Arg Ser Gly
3080                 3085                 3090
Tyr Val  Ile Gln Gly Ser Ser  Asp Leu Ile Cys Thr  Glu Lys Gly
3095                 3100                 3105
Val Trp  Ser Gln Pro Tyr Pro  Val Cys Glu Pro Leu  Ser Cys Gly
3110                 3115                 3120
Ser Pro  Pro Ser Val Ala Asn  Ala Val Ala Thr Gly  Glu Ala His
3125                 3130                 3135
Thr Tyr  Glu Ser Glu Val Lys  Leu Arg Cys Leu Glu  Gly Tyr Thr
3140                 3145                 3150
Met Asp  Thr Asp Thr Asp Thr  Phe Thr Cys Gln Lys  Asp Gly Arg
3155                 3160                 3165
Trp Phe  Pro Glu Arg Ile Ser  Cys Ser Pro Lys Lys  Cys Pro Leu
3170                 3175                 3180
Pro Glu  Asn Ile Thr His Ile  Leu Val His Gly Asp  Asp Phe Ser
3185                 3190                 3195
Val Asn  Arg Gln Val Ser Val  Ser Cys Ala Glu Gly  Tyr Thr Phe
3200                 3205                 3210
Glu Gly  Val Asn Ile Ser Val  Cys Gln Leu Asp Gly  Thr Trp Glu
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3215 3220 3225
Pro Pro Phe Ser Asp Glu Ser Cys Ser Pro Val Ser Cys Gly Lys
3230 3235 3240
Pro Glu Ser Pro Glu His Gly Phe Val Val Gly Ser Lys Tyr Thr
3245 3250 3255
Phe Glu Ser Thr Ile Ile Tyr Gln Cys Glu Pro Gly Tyr Glu Leu
3260 3265 3270
Glu Gly Asn Arg Glu Arg Val Cys Gln Glu Asn Arg Gln Trp Ser
3275 3280 3285
Gly Gly Val Ala Ile Cys Lys Glu Thr Arg Cys Glu Thr Pro Leu
3290 3295 3300
Glu Phe Leu Asn Gly Lys Ala Asp Ile Glu Asn Arg Thr Thr Gly
3305 3310 3315
Pro Asn Val Val Tyr Ser Cys Asn Arg Gly Tyr Ser Leu Glu Gly
3320 3325 3330
Pro Ser Glu Ala His Cys Thr Glu Asn Gly Thr Trp Ser His Pro
3335 3340 3345
Val Pro Leu Cys Lys Pro Asn Pro Cys Pro Val Pro Phe Val Ile
3350 3355 3360
Pro Glu Asn Ala Leu Leu Ser Glu Lys Glu Phe Tyr Val Asp Gln
3365 3370 3375
Asn Val Ser Ile Lys Cys Arg Glu Gly Phe Leu Leu Gln Gly His
3380 3385 3390
Gly Ile Ile Thr Cys Asn Pro Asp Glu Thr Trp Thr Gln Thr Ser
3395 3400 3405
Ala Lys Cys Glu Lys Ile Ser Cys Gly Pro Pro Ala His Val Glu
3410 3415 3420
Asn Ala Ile Ala Arg Gly Val His Tyr Gln Tyr Gly Asp Met Ile
3425 3430 3435
Thr Tyr Ser Cys Tyr Ser Gly Tyr Met Leu Glu Gly Phe Leu Arg
3440 3445 3450
Ser Val Cys Leu Glu Asn Gly Thr Trp Thr Ser Pro Pro Ile Cys
3455 3460 3465
Arg Ala Val Cys Arg Phe Pro Cys Gln Asn Gly Gly Ile Cys Gln
3470 3475 3480
Arg Pro Asn Ala Cys Ser Cys Pro Glu Gly Trp Met Gly Arg Leu
3485 3490 3495
Cys Glu Glu Pro Ile Cys Ile Leu Pro Cys Leu Asn Gly Gly Arg
3500 3505 3510
Cys Val Ala Pro Tyr Gln Cys Asp Cys Pro Pro Gly Trp Thr Gly
3515 3520 3525
Ser Arg Cys His Thr Ala Val Cys Gln Ser Pro Cys Leu Asn Gly
3530 3535 3540
Gly Lys Cys Val Arg Pro Asn Arg Cys His Cys Leu Ser Ser Trp
3545 3550 3555

Thr Gly His Asn Cys Ser Arg Lys Arg Arg Thr Gly Phe
3560 3565 3570

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